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Sexual Precocity, GnRH Analogs, and Growth

Paul A. Boepple, M.D.
Assistant Pediatrician
Reproductive Endocrine Unit
Massachusetts General Hospital
Instructor in Pediatrics
Harvard Medical School
Boston, Massachusetts

William F. Crowley, Jr., M.D.
Chief, Reproductive Endocrine Unit
Massachusetts General Hospital
Assistant Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Exposure of the skeleton during childhood to pubertal levels of sex steroids profoundly increases linear growth and epiphyseal maturation. This is exemplified in the normal state of adolescent sexual development and occurs also in the pathological state of sexual precocity. In the latter, one sees marked acceleration of linear growth, but subsequent epiphyseal fusion results in early cessation of growth. Thus, many children with sexual precocity fall short of their genetic potential for adult height.

The initial goal of this article is to review the normal physiology of the normal role of gonadotropin-releasing hormone (GnRH), which is also known as luteinizing-hormone-releasing hormone (LHRH). A discussion of the impact of pituitary-gonadal suppression on growth and final height in children with central precocious puberty (CPP) with the use of suprapotent GnRH agonist-analogs (GnRHa) will follow.

GnRH, LH, and FSH in Normal and Central Precocious Puberty

Pubertal maturation and adult reproductive function are dependent on a precisely integrated neuroendocrine-gonadal axis. The same neuroendocrine changes that underlie normally timed pubertal maturation are active in CPP. Normal puberty and CPP are both initially characterized by nocturnal, sleep-entrained, pulsatile luteinizing hormone (LH) secretion. This pulsatility probably results from a pulsatile secretion of GnRH. With progression of pubertal maturation, secretion of LH is established in the daytime, and 24-hour patterns of pulsatile LH release, which are characteristic of the adult state, then evolve. The maturation of gonadal function that is induced by LH and follicle-stimulating hormone (FSH) results in the spectrum of physical changes observed at puberty. These changes are the result of both direct and indirect effects of sex steroids.

It is important to remember that the development of normal puberty consists of both gonadarche and adrenarche. The sex steroids produced by the gonads are responsible for gonadarche, which is under the control of GnRH, LH, and FSH. The control of adrenarche is not understood, but it is not under the control of the gonadotropins, adrenocorticotropic hormone (ACTH), or prolactin. Adrenarche is characterized by a significant increase in the secretion of adrenal sex steroids, best indexed by dehydroepiandrosterone sulfate (DHEAS). Interestingly, in CPP, gonadarche is always present, but adrenarche may or may not be present. The reason for this is not understood since the control of normal adrenarche is not understood.

In vitro and in vivo studies in animals and humans have shown that the dose and pattern of GnRH stimulation play critical roles in the pituitary's release of LH and FSH. Pulsatile secretion or administration of GnRH, which produces intermittent stimulation of the pituitary, is an absolute requirement for the generation of pulsatile secretion of gonadotropins. Continuous GnRH stimulation of the gonadotropes induces an initial release of LH and FSH, which subsequently wanes during continued exposure.

Pituitary Desensitization with GnRH Agonist-Analogs

If the level of continuous GnRH exposure is sufficiently high, the pituitary is desensitized and will no longer have the capacity to respond to superimposed boluses of GnRH. The pituitary can be even more significantly desensitized with potent analogs of GnRH. Interestingly, chronic desensitization is not associated with depletion of cell stores of

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hormone, nor with a decreased number of GnRH receptors on the pituitary cell membrane. Responsiveness of the gonadotropes to pulsatile GnRH is fully and rapidly restored when continuous GnRH or analog exposure is withdrawn.

Critical experiments were performed several years ago to chart the physiologic actions of GnRH. The metabolic fate of the native decapeptide in vivo was also determined. These data helped to establish the basis for the synthesis of GnRH analogs that retained biological activity and were relatively resistant to in vivo degradation. The GnRH molecule was modified at the position of the sixth amino acid and the C-terminus. These modifications succeeded in creating a family of compounds with suprapotent agonist properties and the ability to desensitize the pituitary to GnRH pulsation. Thus, the availability of long-acting, suprapotent GnRHa and the emerging knowledge of the action of GnRH were combined. As a result, a role for these analogs was suggested as a possible therapeutic agent in a number of clinical settings in which reversible suppression of the pituitary-gonadal axis is desirable (eg, contraception, prostate cancer, endometriosis, uterine fibroids, and CPP). These compounds and their comparable potencies are listed in Table 1.

Since the specific potency and in vivo clearance rates of GnRH agonists vary considerably, careful attention to dose, frequency of administration, and route of administration is essential. For example, only 5% of intranasally administered analog is absorbed. The reader should understand that utilizing an agonist of low potency, choosing too low a dose, administering doses at an insufficient frequency, or providing a combination of these factors, may result in a failure to induce complete desensitization of the pituitary. In this situation, the administered GnRHa may not act as an inhibitor but as a potent stimulator of pituitary-gonadal function. If this occurs for a prolonged period, the patient's ultimate height may be inadvertently diminished from that expected either normally or with complete suppression of the pituitary-gonadal axis by adequate GnRHa therapy.

The availability of depot formulations of GnRHa that are able to maintain consistent pituitary suppression may serve to obviate some of the above concerns. Regardless of whether a depot or short-acting preparation is used, one can only be sure that the clinically desired suppression has been induced by determining with careful monitoring that the pituitary no longer continues to release LH. The response to a GnRH challenge—therefore, the release of gonadotropins—must be suppressed.

Monitoring is especially critical since one is hypothesizing that the observed endpoints, such as linear growth and maturation of the skeleton in children with CPP, are being measured in a patient who has no sex steroids present. The concentration of gonadal sex steroids must fall to prepubertal levels and pulses must be eliminated even when LHRH is given intravenously. The documentation of prepubertal-sized ovaries and, therefore, gonadal "inactivity" by ultrasound also is of extreme value in demonstrating complete suppression of pituitary and ovarian function in girls with CPP.

A complication of evaluating the suppression of LH sometimes occurs when the radioimmunoassay kits that are used to measure LH also measure the α-subunit of the glycoprotein-tropic hormones of the pituitary. Very interesting, and as yet unexplained, is the fact that the α-subunit continues to be released in patients who are receiving GnRHa. The α-subunit is biologically inactive, but in some LH assays the α-subunit crossreacts with intact LH. In these assays it may appear that the patient does not have total suppression of the pituitary because α-subunit measurements may be mistaken for LH measurements. However, the release of LH itself may be totally inhibited. Evaluation of the results of the LH assay requires knowledge as to whether the α-subunit is measured, as well as intact LH, or whether just LH is measured. The assays used to measure LH following GnRH stimulation in the analog-suppressed patients should be those that measure

Table 1. GnRH and GnRH agonists

pGlu 1	His 2	Trp 3	Ser 4	Tyr 5	Gly 6	Leu 7	Arg 8	Pro 9	NH_2 10		Relative Potency 1 (Standard)
								NEt		(Fujino)	4
					D-Ala						3
					D-Ala			NEt			14
					D-Tyr			NEt			68
					D-Trp			NEt		(Salk)	144
					D-Ser (t-Bu)			NEt		(Hoechst)	(20-40)
					D-Leu			NEt		(TAP)	(20-30)
					D-Nal[2]					(Syntex)	
					D-His (Imbzl)			NEt		(Ortho)	140

intact LH, and the antibodies in these assays should not crossreact with the α-subunit.

The Effect of GnRHa Therapy in CPP on Growth and Skeletal Maturation

Premature exposure of the child to sex steroids causes an acceleration in skeletal maturation that exceeds the acceleration of linear growth. Consequently, in the child with CPP the Δbone age (BA)/Δheight age (HA) is greater than 1.0, and the ultimate height is reduced when this persists. The hypothesis that GnRHa therapy of CPP will increase the ultimate heights implies that suppression of the sex steroids will result in just the reverse: a more pronounced slowing of skeletal maturation than of linear growth (ΔBA/ΔHA will, therefore, be significantly less than 1.0). In this instance, the absence of sex steroids should delay epiphyseal fusion and result in an adult height greater than that which would have been expected if sexual precocity had continued unabated. Several studies, including our own in collaboration with investigators at Children's Hospital in Boston and at the University of Virginia in Charlottesville, have provided preliminary evidence and support of this hypothesis that patients with CPP who are treated with GnRHa may end up taller than they otherwise would have. The crux of success relates to the relative slowing of the advancement of BA in relation to the advancement of HA, and not to the actual increase in linear height each year. If the ΔBA/ΔHA is <1.0 over an extended period, the predicted height and ultimate height should be increased.

In our clinical studies we demonstrated very early that most patients treated with the analog have decreased linear growth compared with their pretreatment growth rates. The Figure, in conjunction with the following explanation, clarifies the variations observed according to the pretreatment skeletal age.

Young children (as exemplified in the left panel of the Figure) whose pubertal development was arrested when their BAs were still in the prepubertal range (ie, ≤10 years) have continued to grow at prepubertal rates. Other children whose therapy began when their skeletal maturations were advanced to late pubertal stages and whose BAs were ≥13 years (right panel), have grown at significantly slower rates than normal children who were matched for chronologic age (CA). The explanations for these observations are as follows: When one considers that the BA of patients in the latter instance is well past the age of peak height velocity growth, the slow growth velocities that are observed can be viewed in an appropriate developmental context. These individuals are growing less rapidly, as expected in relation to normal growth velocity curves. This slow growth rate is not necessarily detrimental to the ultimate height, as it must be viewed along with changes in skeletal maturation that determine whether there ultimately is an increased increment in growth. As predicted, growth velocity during sex steroid suppression is greater in children with BA <10 years than in patients with older BAs.

In a group of 43 girls with CPP who have completed three years of GnRHa therapy in our study, the mean growth velocity fell from 10.9 cm/year prior to therapy to 5.8 cm in the first, 4.8 cm in the second, and 4.2 cm in the third year. In comparing the patients with a pretherapy BA ≤10 when therapy was started with those whose BAs were ≥13 years, one notes that the rate of growth was 6.9 cm/year *v* 4.2 cm the first year. In year two, the com-

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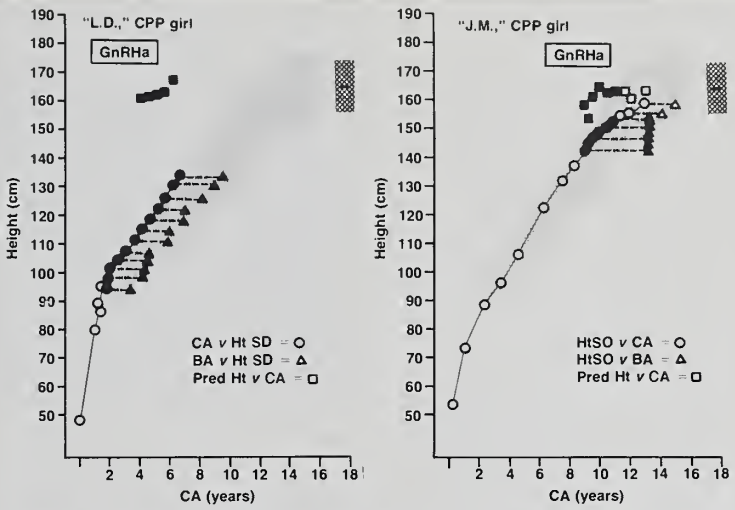

Figure The height charts of two girls with CPP who represent the spectrum of chronologic ages (CA) and bone ages (BA) in our study of GnRHa-induced suppression of gonadal steroids. The left panel depicts data from a girl who began therapy at CA = 1.6 years and BA = 3.3 years. She is now in her sixth year of therapy. The girl whose data are depicted in the right panel began therapy at CA = 9.1 years and BA = 13.2 years. GnRH was discontinued after two years at BA = 13.4 years. These two patients demonstrate several of the issues discussed in the text: (1) the association of growth velocity and BA advancement during therapy (note that growth velocity and ΔBA/ΔCA are significantly greater in the young girl on the left than in the older girl on the right); (2) the increasing predicted height or Ht SD for BA during therapy, which is more striking in the older girl than in the younger girl; (3) the stability of the estimates of predicted height post-therapy (open symbols denote periods pre- and post-therapy, closed symbols: on therapy); and (4) the larger "margin of error" in prediction of adult height in young patients with CPP.

BA = Tanner-Whitehouse RUS bone age; Pred Ht = Bayley-Pinneau predicted height utilizing Greulich-Pyle BA readings; the cross-hatched bar in each panel represents sex-adjusted midparental height ± 9 cm.

parable growth velocities were 6.2 *v* 3.2 cm/year, and in year three, the comparable rates were 5.7 *v* 2.7 cm/year. Regardless of the slow growth velocity in the group with advanced BAs, if the BA remains fixed, as it often does (as exemplified in patient J.M. in the Figure), the increase in growth may equal nearly 9 cm while the BA stays essentially stationary.

The explanation for the slowing of growth when patients with CPP are given GnRHa may relate to the interrelationship of sex steroids and the production of growth hormone (GH). Both estrogen and testosterone have been shown to increase GH secretion in prepubertal individuals. We and others have investigated the effect of GnRHa and, therefore, the decrease of estrogen and testosterone on GH secretion and insulin-like growth factor-I (IGF-I) levels. GH secretion, as determined by integrated concentrations and peak height amplitudes, is diminished in these patients. IGF-I determinations also tend to fall with GnRHa administration, although they usually do not fall into the prepubertal range. Interestingly, adrenarche progresses normally for CA during GnRHa therapy, providing further evidence that adrenarche is not under the control of LH or FSH.

GnRHa Therapy of CPP and the Possible Effect on Final Height

There are no published reports addressing actual final heights in children with CPP who were treated with GnRHa. Consequently, predictions of final height and the impact of therapy upon them must be used. Predictions of adult height using the Gruelich-Pyle BA with the Bayley-Pinneau tables have shown general agreement with subsequent final heights of untreated children with CPP. The use of the Tanner-Whitehouse and Roche-Wainer-Thissen methods of predicting height are not as accurate in children with CPP. Although not ideal, the method of Bayley-Pinneau permits a standardized evaluation of BA (SD for BA) and the probable effectiveness of therapy.

Table 2. Final height prognosis: ht SD for BA

Pretherapy BA	Pretherapy	After 1 year of therapy	After 2 years of therapy	After 3 years of therapy
<10 years	−1.3	−1.5	−1.3	−1.1
10-12 years	−1.9	−2.0	−1.7	−1.7
12-13 years	−2.8	−2.3	−2.1	−2.1
>13 years	−3.7	−3.1	−2.6	−2.1
All	−2.3(80*)	−2.1(83*)	−1.8(68*)	−1.6(43*)

*Number of patients.

During long-term therapy with GnRHa, reports of improvement in the prediction of final heights in children with CPP have been published. Changes in the final height predictions based on SD for BA over three years of therapy are presented in Table 2. These data reveal that patients whose BAs were ≤10 years when therapy was started had only a marginal statistical improvement (the SD score over three years of improvement changed only from −1.3 to −1.1). However, one must, in spite of the marginal statistical improvement, realize that complete suppression of sexual precocity apparently provides tremendous gains for patients in this group. This conclusion is based on the height SD for BA (−3.7) in patients who began therapy at BA > 13 years. The group with the younger BAs could be expected to end up with a comparable SD (−3.7) if they had received GnRHa.

For those whose BAs were ≥13 years when treatment was initiated, the height SD for BA increased from −3.7 to −2.1, a very significant increase. In all groups, the predicted height increased significantly.

Is it advantageous to use the analog until there is complete epiphyseal fusion or is it more advantageous to stop GnRHa therapy earlier than this? One must know the patterns of growth and skeletal maturation during the reactivation of gonadarche to accept that the increments in predicted height during therapy truly reflect an impact on final height. Theoretically, cessation of analog therapy in children with CPP whose BA was ≤11 years (ie, prior to normal peak height velocity) could produce an increased growth rate and a greater ultimate height than if the analog were continued. On the other hand, if the rate of BA advancement was excessive, the patient might lose ultimate height by stopping the analog at such an early BA. Monasco et al have reported data in patients who were followed for one year after the discontinuation of GnRHa therapy. In their report and in our experience, increments in predicted height observed during therapy have not diminished in girls with BA > 13 years.

In a group of such girls whom we

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have followed post-therapy, pubertal function returned when they were far advanced on the declining slope of the pubertal growth spurt. (This was because the BAs were at a mean of 13.6 years.) The average growth velocity in the first year post-therapy in this group neither increased, as might be expected with the resumption of puberty, nor decreased (3.6 cm/year during therapy, 3.7 cm/year post-therapy). The rate of BA advancement with the return of pubertal gonadal function accelerated, with a resultant ΔBA/ΔHA of 0.7 in the first year after therapy. However, significant variability in both growth velocity and BA advancement existed within individuals in the group such that the optimal timing of the discontinuation of GnRHa therapy even in this group is still not known.

Theoretically, children who begin therapy at a young age, and whose BAs are prepubertal when the analog is stopped, might develop an adverse ratio of the ΔBA/ΔHA and lose predicted height. Children in this category who have been withdrawn from therapy at this writing are very few. As these children approach the normal age of puberty, a pubertal growth spurt will be necessary for them to attain the increased height that usually is predicted with the use of GnRHa. It is especially true that in treating this group, we must await the results of further longitudinal studies before the impact of GnRHa therapy on final height in CPP can be fully appreciated. The ideal time to stop the analog therapy remains unknown.

Summary and Conclusions

During suppression of gonadal steroids with GnRHa in patients with CPP the growth velocity correlates inversely with the degree of underlying skeletal maturation. This velocity is similar to that in other hypogonadal states, such as in constitutional delay of puberty with GnRH deficiency. Skeletal maturation proceeds chronologically, year for year, in children with "prepubertal" BAs despite complete suppression of gonadal steroids. However, since gonadal steroids are required for epiphyseal fusion, skeletal maturation virtually ceases in children with CPP whose BAs are in mid-late puberty (therefore, >13 years). Given this ability to forestall epiphyseal fusion, reversible suppression of gonadal steroids permits significant growth to continue at advanced degrees of skeletal maturation.

Like growth rates during gonadal suppression, growth rates during the *reactivation of gonadarche* correlate with the degree of underlying skeletal maturation. The rate of skeletal maturation following the return of pubertal gonadal function is not accelerated. The improvements in the prognosis for the mean final height of the group of patients whose BAs were >13 years that were observed during GnRHa administration are not lost following the discontinuation of therapy. It is unknown at present whether patients whose BAs are less than this will lose predicted height with discontinuation of GnRHa.

Adrenarche, when present in patients with CPP, is not suppressed by administration of GnRHa. The premature secretion of gonadal steroids in CPP, and the subsequent suppression by GnRHa, does not influence the onset, timing, or pace of adrenal androgen secretion. In the majority of patients with CPP, adrenarche develops according to a CA-appropriate secretion of adrenal androgens. Long-term suppression of the pituitary-gonadal axis by GnRH agonists therefore permits investigation of the discrete impact of adrenarche on linear growth, skeletal maturation, and changes in body composition.

The reversible suppression of pituitary-gonadal function, which is induced by GnRHa, permits a clear-cut dissection of the factors affecting childhood and pubertal growth. Therapeutically, GnRH-induced suppression of gonadal sex steroid secretion appears capable of partially reversing the adverse effect that precocious puberty has upon final height. However, close monitoring to assure complete suppression is essential.

An improved understanding of the physiology of growth coupled with the clinical availability of various growth modulators (eg, GnRH, GH, IGF-I) will permit further investigation of the therapeutic implications of the ability to delay the introduction of gonadal steroids in a variety of clinical settings.

Suggested Readings

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In Future Issues

The Morbid and Functional Anatomy of the Human Chromosome Map in Endocrine Disorders and Hormonal Genes
by Victor A. McKusick, M.D.

Assessment and Management of the Psychological Aspects of Short Stature
by Heino Meyer-Bahlburg, Ph.D.

Occult Celiac Disease: A Common Cause of Short Stature
by Asaria Ashkenazi, M.D.

Diagnosis of GHD

This letter is a commentary on the article by Rose et al[1] on the measurement of stimulated *v* spontaneous growth hormone (GH) levels in the diagnosis of growth hormone deficiency (GHD) (abstracted in *Growth, Genetics, and Hormones*, 1988; Volume 4, Number 4).

A hormone, by definition, is "an internal secretion of the endocrine glands, carried by the blood to other organs, where it stimulates them to physiological activity." An unexpected conclusion one may draw from the Rose report is that GH is not a real hormone, since the authors found that normal growth could be documented in children who do not secrete GH; indeed, ten of their normally growing children had integrated GH concentrations (ICGH) (mean GH plasma concentration) as low as the ICGH in GH-deficient children.

The authors pointed out that their results did not agree with two previous studies, one of them by our group,[2] which reported that the 24-hour ICGH in normal children was higher than and did not overlap with that of the ICGH-deficient children. Rose et al stated that we studied only ten prepubertal children and that our observations may "reflect the difference in the pubertal status between the (control and GHD-deficient) groups." This statement is in error. Rose et al ignored our study on the effect of age on the 24-hour ICGH.[3] This is the only study of the ICGH in normal children that included only subjects of normal height as well as normal weight. In this study, we demonstrated that there was no significant difference between the ICGH of normal children who were in stages P1, P2, P3, and P4 of puberty. Only after reaching stage P5 did our normal controls have an increase in the mean ICGH from 5.7 ± 1.4 ($n = 23$) to 7.4 ± 2.0 ($n = 23$) μg/L.[3] We believe that the most likely reason for the difference between our results and those of Rose et al is their unfortunate use of unsatisfactory methods for measuring and deriving the ICGH. They have reported ICGH in the normal control subjects that are often too low and ICGH of GH-deficient children that are always too high.

There are presently two different methods for measuring the ICGH. In the continuous blood withdrawal method, which we introduced in 1971,[4] blood is withdrawn slowly through a nonthrombogenic catheter and collected every half hour over a 24-hour period. Our method has since been used by numerous investigators in the United States and abroad.[5-19] The ICGH is derived by measuring the concentration of GH in a pooled sample from plasma collected during the 24-hour period. The other method, which was used by Rose et al, requires multiple blood withdrawals at short intervals and derives the ICGH by measuring and averaging the concentration of GH in each of the 72 plasma samples collected over a 24-hour period.

We would like to point out several causes for error in the multiple sampling method used by Rose et al:

1. The multiple sampling technique is very stressful to most children, and certainly interferes with their sleep. Donaldson et al[20] studied a group of children by the multiple blood sampling technique on two consecutive nights. They found significant differences between the two measurements in each subject. Two children who did not sleep the first night, but slept soundly during the subsequent night, had second measurements of the ICGH much higher than the first.

We previously reported the results of two consecutive measurements of the ICGH in 36 subjects[3] and we found no significant difference between the two measurements in each subject. We therefore believe that the continuous withdrawal method is less stressful.

2. We have previously demonstrated that the multiple sampling technique underestimates the integrated concentration of any blood constituent that exhibits peaks of concentration at unpredictable times.[21] The reason for inherent error in this technique is that the blood samples may be taken before or after the true peaks. We have also demonstrated that the continuous withdrawal method yielded the true ICGH.[21]

3. We also believe that Rose et al have inadvertently introduced an upward bias to their calculated ICGH in the GH-deficient children. It should be stressed that the secretion of GH is episodic. Several short-lived peaks rise above a basal level, which is usually at the undetectable level of the immunoassay. Most of the 72 blood samples collected from each GH-deficient patient represent such a low baseline. It should be appreciated that at the 0 level of GH, the intraassay variability of any immunoassay is very high. The unbiased results of the immunoassay at the baseline must have a symmetrical distribution around 0. However, the distribution of the GH level used by Rose et al was asymmetrical, since any GH level below 0.5 μg/L was taken as if it were 0.5 μg/L. The result of such a manipulation is an artificially positive ICGH, with a minimum of 0.5 μg/L, even in children who secrete no GH. We believe, therefore, that the ICGH of the GH-deficient patients was overestimated.

4. Rose et al included in their GH-deficient group all children who did not respond to GH stimulation, even those whose growth rate was in the normal range. These children may not have been GH deficient, since we have previously reported cases of children with normal ICGH who were unresponsive to the

GH stimulation tests.[13]

We conclude that the multiple sampling method used by Rose et al was inaccurate. Our continuous withdrawal method has proved to be clinically useful because we have avoided the artifacts that caused the overlapping of the ICGH in the normal and GH-deficient children. We have minimized the stress of the procedure. Because we measure the average concentration of GH in a 24-hour pooled sample, our results in GH-deficient children do not include the upward bias. In normal children, we assay GH at a concentration that is most accurate for the immunoassay.

We also believe that the multiple blood sampling method often leads to a dilution error. The technique requires the emptying of a dead space in the indwelling catheter, which is filled with a heparin solution. A blood sample is then taken from the catheter, which at this point contains undiluted blood. Subsequently, a heparin solution is reintroduced to fill the catheter. To minimize total blood loss, the nurses are instructed not to exceed the dead space of the catheter during the initial emptying of the catheter. If the dead space is too close to the volume taken by the nurse, some diluted blood may remain in the catheter from initial mixing of blood and heparin solution, leading to an artificial lowering of the concentration of hormone in the blood sample. It is possible that the unexpectedly low ICGH readings in the normal control subjects reported by Rose et al were due to unintentional dilution of some of the blood samples.

Finally, Rose et al pointed out the high cost of their intermittent blood withdrawal method. It is important to realize that the high cost was mostly due to the measuring of GH in 72 distinct plasma samples. A considerable cost savings is inherent in our continuous withdrawal method, since we can measure the ICGH in one immunoassay of the pooled sample of plasma that incorporates the continuous blood withdrawal over 24 hours.

A. Avinoam Kowarski, M.D.
University of Maryland
School of Medicine
Johns Hopkins School
of Medicine
Baltimore, Maryland

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To the Editor:

The interesting article by Rose et al[1] proposes that in prepubertal short children the diagnosis of growth hormone deficiency (GHD) be based on abnormal growth hormone (GH) secretory responses to provocative GH-releasing stimuli rather than upon spontaneous GH secretion. We suggest that the provocative and/or endogenous GH secretory data need to be interpreted in the context of the clinical setting, ie, short stature, poor growth velocity, delayed bone age, etc. For example, one might question the diagnosis of GHD in some of their patients who were growing as rapidly as 10 cm/year.

Although a subnormal GH secretion was reported in response to provocative tests, such responses may occur in normal children. Using the same stimulation tests as Rose et al, Root and Russ[2] reported that 2 out of 20 (10%) nonhypopituitary short children had peak GH responses $\leq$7.0 μg/L, and 4 of 20 (20%) had peak GH responses $<$10 μg/L, evidence that false-positive results may occur despite using two or more stimulation tests of GH secretion.

More information about the child or children in the Rose et al study with "relative" tall stature and normal growth velocity(ies) up to +1.5 SD in height and +1.1 SD in growth rate would be of interest. How many GH-deficient children in their study had such normal growth velocities?

Ideally, patients with the absence of the gene for GH or with radiographic evidence of structural disease of the hypothalamic-pituitary axis or multiple anterior pituitary hormone deficiency should be classified as clearly GH-deficient subjects for comparison with other short children. It would have been of interest if Rose et al had included provocative testing of the normal-statured children because, in the past, "short control" children have been the basis for almost all control data.

We also would be interested to learn whether using the statistical methodology of logarithmic trans-

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formation in regard to provocative testing, as Rose et al have done for endogenous testing, would have altered the sensitivity and discriminatory ability of provocative tests. Hindmarsh et al[3] emphasized the overlap of peak GH secretion after insulin-induced hypoglycemia.

Rose et al measured the number of GH pulses and mean GH-pulse amplitude. Were there any abnormalities observed in the pattern of pulsatile secretion of the six children with abnormal provocative tests who had "normal" mean 24-hour GH concentrations? Measurement of a mean 24-hour GH concentration without assessment of the pulsatile pattern of GH secretion may obscure neurosecretory abnormalities.[4]

Our interest in examining endogenous GH secretion and describing GH neurosecretory dysfunction as part of the spectrum of GHD[5-7] results from the observations of many investigators[8-10] who demonstrated that provocative testing, using an arbitrary GH peak cutoff of 7 or 10 μg/L, did not identify all children in whom there was acceleration in growth velocity after exogenous GH therapy.[11] We recognize that endogenous GH secretory studies are not practical in many clinical settings, but they do offer a valuable research tool for assessment of endogenous GH secretion and its regulatory factors. The diagnosis of GHD is difficult, but to exclude studies of endogenous GH secretion in the appropriate patient in the pertinent clinical situation is premature.

Barry B. Bercu, M.D.
Allen W. Root, M.D.
Dorothy I. Shulman, M.D.
Bessil Spiliotis, M.D.
University of South Florida
All Children's Hospital
St Petersburg, Florida

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Authors' Replies

In response to Dr. Kowarski's letter:

Dr. Kowarski draws the conclusion that growth hormone (GH) is "not a real hormone" because some of the normally growing children in our report[1] had mean 24-hour GH levels that overlapped those of GH-deficient children. However, our observation is entirely analogous to the observation of primary hypothyroidism, confirmed by plasma thyroid-stimulating hormone (TSH) elevation, with plasma thyroxine and free thyroxine levels that are within the normal range. The fact that a hormone level is within the normal range for the population does not imply that the level must be normal for a particular individual. For example, a patient whose free thyroxine level is ordinarily at the 80th percentile for the normal population may develop clinical and biochemical evidence of hypothyroidism when this level is reduced to the 20th percentile by thyroid disease.

Dr. Kowarski's data concerning the timing of increased GH secretion during puberty conflict with our own observations.[2] In a study of 145 pubertal normal volunteers who were of normal height and weight, we observed a significant increase in the mean plasma 24-hour GH level by pubertal stage 2 in the girls and by pubertal stage 3 in the boys.

We agree with certain of the differences that Dr. Kowarski notes between the integrated and multiple sampling procedures.[3] However, we find it difficult to believe that these factors would cause both an underestimate of the GH levels in normal subjects and an overestimate of the levels in GH-deficient subjects. Additionally, these technical factors would not explain the difference between our results and those of Bercu et al,[4] who also used a multiple sampling procedure. We conclude that a more likely explanation for the different observations is our emphasis on rigorous matching of pubertal stage between patient and control subjects.

We do not agree with all of the points raised by Dr. Kowarski concerning multiple sampling methodology. First, we are not aware of any direct comparison between the two techniques, in the same children, that has established one approach to be more or less stressful than the other. In our unit, the children do sleep through the procedure. Sampling is done without a tourniquet and does not ordinarily disturb a sleeping child unless he or she is lying on top of the withdrawal site. We purposely chose not to monitor sleep by EEG because this procedure itself disturbs sleep and requires a period of adjustment.

Second, we disagree that the multiple sampling technique has a bias toward underestimation. This technique samples all concentrations in direct proportion to

the probability of their occurring during the total period of blood withdrawal. The fundamental equivalence of these approaches is evident by considering the situation in which the sampling frequency approaches infinity. We do agree, however, that the mean GH level by multiple sampling may be greater or less than would have been observed by the continuous withdrawal method over the same 24-hour period. Further study would be required to determine whether these differences are clinically significant.

Third, the decision to treat undetectable levels as if they were 0.5 μg/L causes a similar upward bias for the normal as well as for the GH-deficient series, since the majority of samples in both groups have GH levels below the assay detection limit.

Fourth, our sampling procedure allows for additional blood (0.1 mL) beyond the dead space volume to prevent sample dilution. Finally, we question the accuracy of single GH radioimmunoassay measurements near the low end of the dose-response curve. We agree that cost savings could be achieved by fewer measurements on pooled samples, but for research purposes we chose to measure all samples to preserve information about the frequency and amplitude of GH peaks.

In response to Dr. Bercu's letter:
We agree that the diagnosis of growth hormone deficiency (GHD) should be made in the context of the clinical setting. All but three of the GH-deficient children were growing at a rate of less than 4 cm/year. The remaining three children fully met other clinical criteria for GHD; for example, the one child with GHD who was growing at 10 cm/year was 13 months old and had deficiencies of all pituitary hormones. Analysis of data led to the same results and interpretation with or without these three patients.

We disagree that only GH-deficient children who lack the GH gene or have panhypopituitarism should be used to evaluate tests for GHD. Such children represent the most severely GH-deficient subjects and are therefore easiest to diagnose. Many short children with isolated GHD have some persisting GH secretion, and it is these children who present the most difficult diagnostic challenge.

We agree that better normative data for the stimulation tests are needed. However, the principal conclusions of our study were not altered by the use of different criteria for normal response to a GH stimulation test.

We found no difference between the pulsatile GH pattern in normal children and in the pulsatile GH pattern in children with decreased stimulation tests and normal mean 24-hour levels. Three of the patients had one, two, or three peaks at night but so did three of the normals. Seven of the patients had peak amplitudes less than 4, but so did four of the normals.

We originally pursued studies of spontaneous GH secretion in the hope that it would have greater sensitivity for the diagnosis of GHD. However, we observed markedly reduced diagnostic sensitivity of the mean 24-hour GH level compared with the GH stimulation tests. Thus, unless future research identifies settings in which this difficult and expensive procedure is more useful, we conclude that its routine use as a method to diagnose GHD is unwarranted.

Susan R. Rose, M.D.
Fernando G. Cassorla, M.D.
Gordon B. Cutler, Jr., M.D.
Developmental Endocrinology Branch
National Institute of Child Health and Human Development
Bethesda, Maryland

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Dr. Blizzard's Reply:

The issue regarding whether there is value in performing an integrated concentration in diagnosing GHD remains contestable. Rose et al, as presented in their article, believe not, while Kowarski et al and Bercu et al believe so. Readers of *Growth, Genetics, and Hormones* will have to decide for themselves whether the existing information about this topic is adequate for them to make a diagnosis.

I am sure that there is agreement regarding the role of integrated concentrations in research studies. In such studies, pulse analyses should accompany analysis of the mean value of GH concentration.

Address for Correspondence

Please send all correspondence to:

Robert M. Blizzard, M.D.
Department of Pediatrics
University of Virginia
School of Medicine
Charlottesville, VA
22908.

Subject Review:
GH Neuroregulation and Its Alterations in Disease States

William L. Clarke, M.D.
Associate Editor
Growth, Genetics, and Hormones

Dieguez et al have recently reviewed the neuroregulation of growth hormone (GH) secretion in great detail. Their article (*Clin Endocrinol* 1988;28:109-143) does not introduce new data but stresses the many advances in the understanding of GH regulation made since the discovery of GH-releasing hormone (GHRH).

A discussion of GH regulation by neuropeptides includes a review of the interaction of GH with somatostatin, opioid peptides, thyrotropin-releasing hormone, and other neuropeptides. A section on peripheral feedback signals describes the influence of growth factors, thyroid hormones, and glucocorticoids that act at the hypothalamic and/or pituitary level. A section on neurotransmitter regulation of GH secretion summarizes a great deal of information concerning the roles of acetylcholine, catecholamines, serotonin and melatonin, histamine, and γ-aminobutyric acid.

The article concludes with a discussion of the diagnostic and therapeutic implications of this information. Acromegaly and its treatment, and GH deficiency and its treatment with GHRH are described. Studies reporting GH secretion and its response to GHRH in diabetes, obesity, psychiatric illness, and other diseases are also explored.

This long review article is current and well documented; it is recommended reading for those interested in the mechanisms of GH secretion in normal and disease states.

Special Report:
David W. Smith Workshop on Malformations and Morphogenesis, August 3-7, 1988, Oakland, California

Judith G. Hall, M.D.
Associate Editor
Growth, Genetics, and Hormones

The theme of this year's workshop was the relationship between dysmorphology and metabolic disease. Inborn errors of morphogenesis are likely to arise from alterations in the biochemistry of development, and it is therefore expected that inborn errors of metabolism will provide clues to developmental processes. The search for these clues has been fueled by the recently recognized association between many peroxisomal disorders (ie, deficiencies of enzymes found in peroxisomes) and developmental anomalies such as renal cysts, retinal dysplasia, malmigration of neurons, stippled epiphyses, and unusual facies.

Drs. Kay Johnson and Stephen Bamforth presented evidence that many, if not all, infants with pyruvate dehydrogenase deficiency, nonketotic hyperglycemia, and congenital lactic acidosis have structural anomalies of the central nervous system, including agenesis and hypoplasia of the corpus callosum, ventriculomegaly with loss of white matter, and apparently nonspecific malmigration of neurons. Drs. John Graham and Cynthia Morris demonstrated cardiac anomalies, nonspecific facial anomalies, and hypotonia with secondary changes in bones in some individuals with defective fatty acid oxidation. These types of anomalies should prompt aggressive metabolic workup.

While it is well recognized that recreational use of cocaine, which has been increasing in North America, can lead to a number of health problems for adults, Drs. Gilberto Chavez and Eugene Hoyme showed that maternal use at any time during fetal development can also lead to vascular accidents in the embryo or fetus. They reported an increase in genitourinary or gastrointestinal and limb reduction anomalies secondary to vascular compromise in utero. The exact incidence and dose relations in humans have not yet been defined.

Molecular approaches to dysmorphology are beginning to yield new information. Dr. Holly Ardinager found a significant association between particular alleles of transforming growth factor alpha (TGFA) and nonsyndrome cleft lip and cleft palate. Dr. Jon Zonana demonstrated close linkage of X-linked hypohydrotic ectodermal dysplasia to a particular restriction fragment length polymorphism (RFLP) marker on Xqi. Interestingly, Dr. Jim Bartley failed to find a detectable molecular deletion in five families with the X-linked Norrie disease even though the exact location of the deletion has been identified.

Dr. Kathy Sulik reviewed the embryology of the abdominal viscera, pointing out that major migrations from the branchial arch system and the cranial endoderm accounted for these organs. She noted that the formation is complete by eight weeks. The growth factors that play a role locally have just begun to be investigated and defined.

Many new syndromes and methods to define them were described. Dr. Roger Williamson described the use of magnetic resonance imaging (MRI) to define the fetus in utero, and Dr. Andy Poznanski elaborated on new uses for hand pattern profile analysis. He explained how the test could be used to evaluate age-associated hand changes in specific syndromes.

At one session, the Rubenstein-

Taylic Syndrome Symposium, Drs. Rubenstein and Taylic presented a historical overview of the syndrome; the natural history was described by several groups. As with other syndromes, this one "changes" with age and looks somewhat different clinically in different ethnic groups. By definition, affected individuals have broad toes and/or thumbs. Perhaps the most useful facial feature is a long columella that protrudes and attaches below the alae nasi. Dr. Roger Stevenson presented a tantalizing case of 7q21-3 deletion that was associated with Rubenstein-Taylic syndrome in one family. Although it has generally been hypothesized that the syndrome is most likely due to a small chromosomal deletion, no consistent evidence of this has been found as yet.

Abstracts From the Literature

Serum IGF-I and Serum Growth-Promoting Activity During the First Postnatal Year in Infants with IUGR

Twenty-one infants with intrauterine growth retardation (IUGR) were followed from birth to age 12 months. Serum insulin-like growth factor-I (IGF-I) was measured by radioimmunoassay. The bioassayable growth-promoting activity of the serum was measured as the thymidine activity (TA) on lectin-activated lymphocytes at ages 5 days and 1, 3, 6, 9, and 12 months, and was compared with control values. Based on their length at age 12 months, the infants with IUGR were divided into three groups: at or above the average (group A, n = 8); between the mean and −2 SD (group B, n = 7); and less than −2 SD (group C, n = 6). No differences in nutritional indices or in head circumference were found among the three groups.

IGF-I levels (Figure 1) were significantly lower at 5 days of age in IUGR infants than in controls. Levels increased slowly in groups A and B and reached the control values at ages 9 and 12 months. Levels in group C remained significantly subnormal at 12 months of age.

TA (Figure 2) was also significantly lower at age 5 days in infants with IUGR compared with controls. It increased sharply at age 1 to 3 months in groups A and B, but remained significantly lower in group C through 12 months.

Individual values of IGF-I and TA were closely correlated; the increase in body length during the first postnatal year correlated sig-

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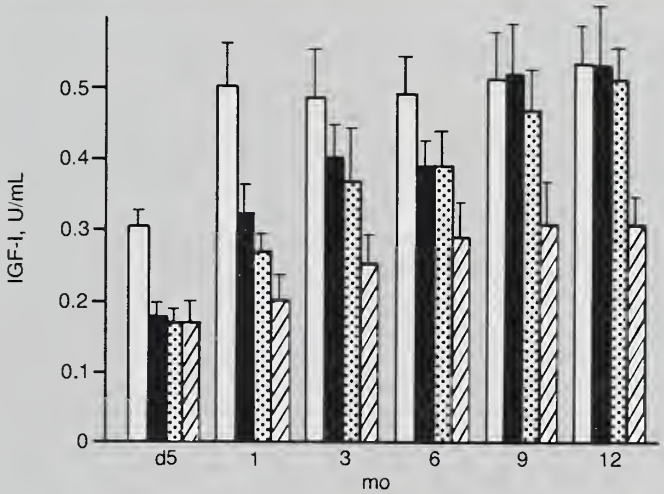

Figure 1 Somatomedin C /IGF-I mean and SEM values from 5 days to 12 months in controls (*open bars*), group A (*closed bars*), group B (*dotted bars*), and group C (*hatched bars*) IUGR patients.

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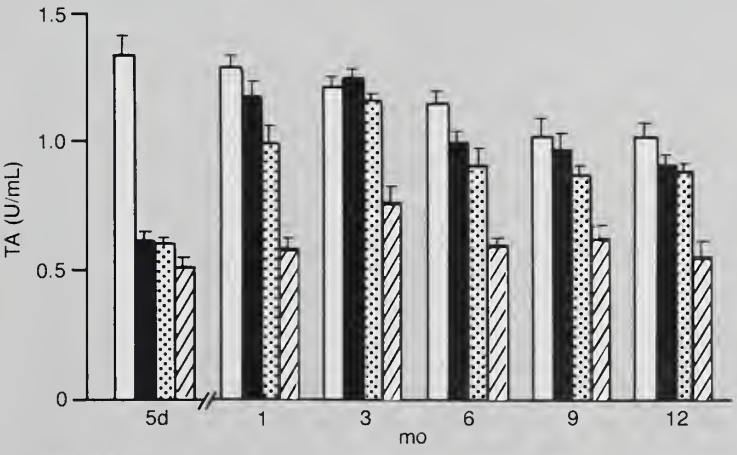

Figure 2 TA mean and SEM values: *symbols* are the same as in Figure 1.

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Serum IGF-I and Serum

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nificantly with the TA levels at 1 and 3 months, but not with the IGF-I levels at 1, 3, and 6 months. These data may be of some physiologic significance in understanding the postnatal catch-up growth that occurs after IUGR.

Thieriot-Prevost G, Boccara JF, Francoual C, et al. *Pediatr Res* 1988;24:380-383.

Editor's comment—*These authors contributed significantly to our understanding of what happens to IGF-I and growth-promoting activity as measured by TA during the first year of life. Their goal was to follow the evolution of IGF-I and growth-promoting activity concentrations and determine whether they correlated with growth. Their findings will be useful in other studies. For example, could failure of growth-promoting activity to increase at 1 and/or 3 months—as seen in group C—indicate responsiveness or unresponsiveness to growth hormone given under a standardized protocol?*

Robert M. Blizzard, M.D.

Copies of back issues of *Growth, Genetics, and Hormones* are available and will be sent to readers who request them. Simply note the issue number(s) on a postcard (or your letterhead) and mail to Ms. Patti Galati, McGraw-Hill Healthcare, 800 Second Avenue, New York, NY 10017.

Copper Deficiency Impairs Growth of Infants Recovering from Malnutrition

Malnourished infants who receive milk-based formulas with low copper content and who experience episodes of diarrhea are at risk for developing copper deficiency. However, the routine treatment modalities for malnourished infants often do not address the potential for copper deficiency and its effect on growth and nutritional rehabilitation.

To evaluate the effect of copper deficiency on growth, the investigators studied 11 copper-deficient infants who were inpatients at a nutrition recovery center in Chile. All had low plasma copper levels (<70 μg %) and ceruloplasmin (<200 mg/L); three had neutropenia (neutrophil count <1,500/mL). These infants were compared with "control" infants (with malnutrition, but no copper deficiency) who were matched for age, sex, birth weight, weight for length, and mean stay at the center. Growth was evaluated one month before and one month after copper supplementation in both groups. Copper sulfate was given at a dose of 80 μg/kg/day for 30 days. Supplemental vitamins and 1-2 mg/kg/day of elemental iron were also administered. Infants were fed ad libitum every four hours by caretakers who where blinded to their copper status.

In the copper-deficient group, plasma copper and ceruloplasmin levels increased after one month of copper supplementation ($P<0.001$) and all but one infant achieved normal plasma copper levels >90 μg %. The control group maintained normal biochemical indices of copper status throughout.

Although weight-for-length and length-for-age values were similar in both groups, the copper-deficient infants had a lower weight-for-age ($P<0.05$) at the onset of the study. After copper supplementation, weight-for-age and weight-for-length values were significantly improved in the copper-deficient infants. These infants also demonstrated a greater rate of weight gain after supplementation than before supplementation (4.8 *v* 3.6 g/kg/day) and as compared with the control group (4.8 *v* 2.4 g/kg/day). The acceleration in weekly weight gain occurred by the second week of copper supplementation and was maintained in the copper-deficient group. However, the control infants had a gradual decline in relative weight gain over time.

Castillo-Duran C, Uauy R. *Am J Clin Nutr* 1988;47:710-714.

Editor's comment—*The authors interpreted the data to show that copper supplementation improves growth of copper-deficient infants recovering from malnutrition. However, all infants in the study, regardless of their copper status, demonstrated improved weight gain while receiving >150 kcal/kg/day for catch-up growth. Even the copper-deficient infants gained weight without copper supplementation—as did the control infants—during the two-month evaluation period at the nutrition recovery center ($P<0.1$, t test; editor's statistic). The fact that the control group did not maintain an accelerated weight gain, as observed in the copper-deficient group, may be attributed to differences in the degree of malnutrition. The copper-deficient infants were more severely malnourished than the controls; this explains their need to continue to gain weight at an accelerated rate for a longer period of time.*

Although the authors report that these infants did not have zinc deficiency, no information is presented on mineral status before and after study entry. Also, one cannot exclude the impact of iron and/or vitamin supplementation on the recovery of these infants. Thus, the role of copper supplementation alone on improving growth is cloudy. However, the recognition and treatment of this problem are important because copper has other important physiologic implications that are not growth-related.

Fima Lifshitz, M.D.

The Frequency of Genetic Disorders in Children and Young Adults

Utilizing the British Columbia Health Surveillance Registry, a survey was taken of more than one million consecutive births to determine the frequency of genetic diseases in individuals younger than 25 years of age. The survey revealed that 5.3% of individuals develop a disease with an important genetic component. Of the 5.3%, 0.36% are single-gene disorders and 4.6% are clearly defined multifactorial disorders such as cleft lip or diabetes.

The survey was carefully designed to exclude congenital anomalies that were thought to be nongenetic in origin. If data for all congenital anomalies were included in the tabulation, 7.9% of individuals could be identified as having either a congenital anomaly or a known genetic disorder. A further breakdown of the single-gene disorders gives an incidence of 1.4 per 1,000 for autosomal dominant disorders, 1.7 per 1,000 for autosomal recessive disorders, 0.5 per 1,000 for X-linked disorders, and 1.8 per 1,000 for chromosomal abnormalities. Adult-onset diseases were not included in this survey.

It is quite clear from the study that genetic disorders occur very frequently if grouped together, although each individual disorder is relatively rare.

Baird PA, Anderson TW, Newcombe HB, et al. *Am J Hum Genet* 1988;42:677-693.

Editor's comment—*This survey is very useful because it gives a handle on the incidence and frequency of genetic disorders in the general population. It provides the kind of information that policy makers and healthcare planners need.*

Judith G. Hall, M.D.

Knemometry in Childhood: Accuracy and Standardization of a New Technique of Lower Leg Length Measurement

The authors carried out a study of the accuracy of lower leg length measurement by the apparatus introduced some five years ago by Valk and his colleagues. Ninety subjects between the ages of 2.4 and 17.1 years were involved; 46 were referred because of tall or short stature and 44 were normal. Six measurements were taken from each subject at each measurement session; the total number of measurement sessions was 2,200. Subjects and apparatus were displaced and repositioned between each measurement.

The ranges within the six measurements were 0.1 mm (rare) through 0.3 and 0.4 mm (very common) to 1.0 mm, with a few measurements beyond 1.0 mm. Using the median instead of the mean, the average SD of a single estimation was 0.16 mm. When differences between each of the six measurements and the medians of all six were examined, it was clear that the first of the six measurements was both biased and unreliable; when it was dropped, the SD decreased to 0.13 mm. Moreover, when only four measurements were taken and the first discarded, the results were as reliable as when the six measurements were taken and the first discarded. The procedure now recommended for future studies, therefore, is to take four measurements, discard the first, and average the next three.

Although its effect disappears in about two hours, exercise immediately before the lower leg length measurement is taken seems to reduce the measurement in children; strangely, it produces the opposite effect in adults. Therefore, vigorous physical activity should be avoided before measurements are taken. However, the child should be instructed to stand or walk slowly for five to ten minutes before being measured to provide standardized loading to the lower leg; sitting should not be allowed.

Twelve children were measured on successive days. Over 24 hours the average gain in lower leg length was 0.67 mm, with a range of approximately 1.5 mm to −1.5 mm. Most of the children were also measured weekly and straight lines were fitted to each individual's series of measurements over a period of six months. Deviations among these lines greatly exceeded amounts that could be attributed to measurement error. Thus, the authors state that "estimates of growth velocities of the lower leg on the basis of two measurements taken some weeks apart...are barely reproducible." However, longitudinal *series* of measurements on individuals, taken weekly over long periods, are a very useful way to investigate growth.

Hermanussen M, Geiger-Benoit K, Burmeister J, et al. *Ann Hum Biol* 1988;15:1-16.

Editor's comment—*This is the definitive study, to date, of the reliability of the Valk technique for lower leg length measurement. The results speak for themselves. The four-measurement technique, in which the first is discarded and the next three averaged, should be adopted as standard. The accuracy of a given measurement is then high; however, due to fluctuations in growth rates, differences between two short-term velocities are unreliable. This conclusion agrees with that of Wales and Milner (abstracted in* Growth, Genetics, and Hormones, *Vol. 4, No. 1). Anyone using the Valk knemometer or a similar apparatus should read this article before embarking on clinical studies.*

James M. Tanner, M.D., D.Sc.

Periodic Changes of Short-Term Growth Velocity ('Mini Growth Spurts')

Lower leg length was measured in 73 healthy children, ages 2.7 to 15.9 years, 18-106 times by the Valk machine once or twice a week. The standardized technique described in the abstract on knemometry (see p 13) was used. Straight lines covering three to four successive points were fitted to each 31-day period of each child. Rolling monthly average rates for each child were then computed (just as rolling annual velocities are calculated for stature when measurements are taken every three or six months). These rolling monthly rates were then plotted for each child on a day-by-day basis: the mean of the observations during days 1-31 was recorded, then the mean for days 2-32, and so on.

The deviations of the actual measurements from these individual curves showed significant clustering above or below the line in 38 of the 73 curves, and a characteristic up-and-down pattern of growth velocity was found in 45 curves. The investigators referred to these variations as "mini growth spurts." The peaks have a velocity of about two to three times that of the troughs, and occur between 30 and 55 days apart. There was a significant correlation between the stature of the child and the frequency of his mini growth spurts.

Growth troughs coincided often with periods of intermittent infectious illnesses, but only a small percentage of the mini growth spurts could be explained as catch-up growth after this type of growth arrest. The reason for the majority of these spurts is unknown.

The authors conclude that "monitoring the pattern of short-term growth kinetics by multiple longitudinal knemometric measurements may provide an additional and very sensitive tool to control therapeutic regimes."

Hermanussen M, Geiger-Benoit K, Burmeister J, et al. *Ann Hum Biol* 1988;15:103-109.

Editor's comment—*This paper extends the observations noted in the abstract on knemometry. Many perfectly healthy children seem to have fluctuations in the growth rate of their tibial epiphyses, with peak-to-peak periods of approximately 30 to 50 days. Elucidation of the physiology of this phenomenon will be awaited with the greatest interest. Do such spurts occur in all the long bones at once, or do they alternate from one long bone to another (as was alleged by Godin and others in the early years of this century)? Rats have a tibial epiphyseal cell cycle time of two to three days; humans, about 20 days. Do mini growth spurts occur several days apart in the rat tibia? From a clinical point of view, the authors throw cold water (not for the first time) on the short-term use of short-term velocities. But they very correctly point out that the* long-term *use of short-term velocities—a daunting task for patient and anthropometrist alike—might yield very valuable information. This phenomenon seems to be analogous to the pulsatile secretion of hormones.*

James M. Tanner, M.D., D.Sc.

Uniparental Disomy as a Mechanism in Human Diseases

Although an individual normally inherits one of each pair of chromosomes from mother and one from father, very rarely there is an individual who has inherited both chromosomes of a pair from only one parent. This phenomenon is known as uniparental disomy. Although it has been previously demonstrated in animals, the report by Spence et al marks the first time that uniparental disomy has been demonstrated by DNA studies in a human being with normal chromosomes. The affected individual, a girl with cystic fibrosis, inherited both of her number 7 chromosomes from her mother. Nonpaternity was confirmed by numerous other markers. Thus, in that particular family, the probability of the proband's having a child affected with cystic fibrosis is reduced from the usual 25% to nearly zero.

Interestingly, this girl also had intrauterine growth retardation (IUGR). The observation of uniparental disomy suggests that it may occur for other chromosomes and for other diseases. The evaluation of families by studies in molecular genetics now makes it possible to recognize this type of mechanism. It seems likely that uniparental disomy is responsible for autosomal recessive diseases only rarely, probably accounting for less than 1% of individuals with apparent autosomal recessive inheritance. However, the clue to such cases may be the presence of IUGR.

Spence JE, Perciaccante RG, Greig GM, et al. *Am J Hum Genet* 1988;42:217-226.

Editor's comment—*Nothing is sacred anymore. Things as basic as Mendel's peas have exceptions. For the geneticist, however, exceptions serve as incentives to learn more about normal mechanisms of inheritance. At this point, we do not yet know how "normal" uniparental disomy is.*

Judith G. Hall, M.D.

In Future Issues

Gonadotropin and Steroid Concentrations in the Fetus and Newborn, by Claude Migeon, M.D.

The Remarkable Catch-up Growth in American Slaves by Richard H. Steckel, Ph.D.

Growth in Late Adolescence, by Alex Roche, M.D.

April 12-16 15th Training Course on Hormonal Assay Techniques. Holiday Inn, Bethesda, Maryland. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

April 27-30 Lawson Wilkins Pediatric Endocrine Society Review Course in Pediatric Endocrinology. Hyatt Regency Washington on Capitol Hill, Washington, D.C. Contact: Beverly Wellman, Serono Symposia, USA, 280 Pond Street, Randolph, MA 02368 (800-225-5185)

April 27-30 Biennial Meeting of the Society for Research in Child Development. Kansas City, Missouri. Contact: Kathleen McCluskey-Fawcett, Ph.D., Department of Psychology, University of Kansas, 426 Fraser Hall, Lawrence, KS 66045-2160 (913-864-4131)

May 1-5 Annual Meeting of the American Pediatric Society/Society for Pediatric Research/Ambulatory Pediatric Association. Washington Sheraton, Washington, D.C. Contact: Debbie Wogenrich, Executive Director, Society for Pediatric Research, 2650 Yale Boulevard S.E., Suite 104, Albuquerque, NM 87106 (505-764-9099)

May 5 Annual Meeting of the Lawson Wilkins Pediatric Endocrine Society. Washington Sheraton, Washington, D.C. Contact: Gilbert August, M.D., Department of Endocrinology, Children's Hospital, National Medical Center, 111 Michigan Avenue N.W., Washington, D.C. 20010 (202-745-2121)

June 3-6 Annual Meeting of the American Diabetes Association. Detroit, Michigan. Contact: American Diabetes Association, 1660 Duke Street, Alexandria, VA 22314 (703-549-1500 or 800-ADA-DISC)

June 21-24 71st Annual Meeting of the Endocrine Society. Seattle Convention Center, Seattle, Washington. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

June 25-28 2nd International Pituitary Congress. Marriott's Desert Springs, Palm Desert, California. Contact: Grace Labrado, Department of Endocrinology, Cedars Sinai Medical Center, Room B-131, 8700 Beverly Boulevard, Los Angeles, CA 90048 (213-855-4691)

September 23-25 30th Annual Meeting of the American College of Nutrition. Omni International Hotel, Norfolk, Virginia. Contact: Kay Balun, Administrative Assistant, American College of Nutrition, 345 Central Avenue, Suite 207, Scarsdale, NY 10543 (914-723-4247)

October 11-14 41st Annual Postgraduate Assembly of The Endocrine Society. Fairmont Hotel, New Orleans, Louisiana. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

October 29-November 3 Joint Meeting of the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology (scientific sessions, October 30-November 1). Jerusalem Hilton, Jerusalem, Israel. Contact: Zvi Laron, M.D., Beilinson Medical Center, Petah Tikva 49 100 Israel

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Robert M. Blizzard, M.D.
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Occult Celiac Disease: A Common Cause of Short Stature

Asaria Ashkenazi, M.D.
Associate Professor of Pediatrics
Director, Department of Pediatrics B
Kaplan Hospital, Rehovot
Affiliated with the Medical School of the Hebrew University and Hadassah
Jerusalem, Israel

Failure to thrive in association with gastrointestinal (GI) symptoms is common in children with active celiac disease (CD). In two studies[1,2] of patients with GI symptoms due to CD, 36% and 55% were below the third centile for height, and 40% and 60% were below it for weight. A small proportion (~5%) of CD patients with short stature, however, have no GI symptoms. They are considered to have occult CD, which is quite important in the differential diagnosis of short stature.

Etiology and Pathogenesis of CD

Wheat gluten, specifically its gliadin fraction, is toxic to genetically susceptible individuals. In recent studies, we demonstrated the toxic effects of purified gliadin derived from peptides; it was obtained from intestinal mucosa cultures of CD patients ingesting a normal gluten-containing diet. The smallest toxic peptide had a molecular mass of 6,129 daltons and contained 53 amino acids.

Although gliadin-toxic peptides damage the intestinal mucosa in genetically susceptible individuals, the exact mechanism is not completely understood.[3-5] Current opinion favors the hypothesis that the harmful effects of gluten are mediated by immunologic processes. Immunologic reactions appear to play a part in the pathogenesis of CD, but the distinct mechanism—be it cellular immunity, humoral immunity, or a combination of the two—remains elusive.[6]

Short Stature as the Presenting Symptom of CD

Several investigators have reported short stature as the only manifestation in some cases of CD (Table).[7-11] In one cohort[7] of 796 children and adolescents seen for growth retardation, 14 had CD (1.8%). Although the children with CD had no current GI symptoms, eight had a history of diarrhea during infancy. In another study, 34 patients with short stature of undetermined origin, but no GI symptoms, underwent jejunal biopsy for exclusion of celiac disease.[8] Eight patients (24%) had subtotal or severe partial villous atrophy; seven of these patients showed significant increases in height and weight velocity after switching to a gluten-free diet.

In a group of 108 children with short stature of undetermined etiology referred to an endocrine clinic in Italy, 9 (8%) had CD.[9] All patients with CD were diagnosed by a biopsy of the small intestine, and the specimen was obtained via the oral route. The investigators found that although no single screening test or combination of tests identified all of these patients, an abnormal xylose test, the presence of antireticular and/or antigliadin antibodies, and a history of diarrhea in the first 2 years of life identified most cases of CD. In a similar study,[10] 87 children with short stature (height > 2 SD below the mean for age and sex) underwent biopsy of the small intestine after other causes of growth retardation had been ruled out. Although none had GI symptoms, four (5%) had CD.

Another study, conducted in Israel, described short stature as a major manifestation of CD in older children.[11] In 11 of 23 (48%) patients referred to a gastroenterologist after an extensive negative endocrine evaluation, CD was diagnosed by small-bowel biopsy.

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No clinical or laboratory clues enabled the investigators to differentiate between the cases of short stature due to occult CD and those due to other causes. Equally unhelpful in differential diagnosis was the age at diagnosis, length of follow-up prior to referral to the GI service, and degree of bone-age retardation. Although abnormal stool-fat excretion was found only in children with CD, sensitivity was low, and abnormal results were found in only four of nine patients tested. However, testing for the presence of microcytic anemia revealed that all of the children with CD, but none without the disease, were anemic. A positive history of past GI problems, particularly diarrhea, during early childhood also was very helpful.

The prevalence of CD is low in some studies (1.8%,[7] 8%,[9] and 5%[10]) but high in others (24%[8] and 48%[11]). This disparity may indicate that CD can be recognized and treated in some areas of the world at a younger age, when the malabsorption symptoms are more clear-cut and before severe stunting of growth occurs; in other regions, however, it tends to be diagnosed later, when short stature is the more obvious problem. This varying prevalence may also reflect a real disparity between the incidence of CD and its mode of presentation.

Table. Reports of the prevalence of CD in children with short stature

Study	Year	Total no. studied	No. with CD
Verkasalo et al, Helsinki[7]	1978	796	14 (1.8%)
Groll et al, London[8]	1980	34	8 (24%)
Cacciari et al, Bologna[9]	1985	108	9 (8%)
Stenhammar et al, Sweden[10]	1986	87	4 (5%)
Rosenbach et al, Tel Aviv[11]	1986	23	11 (48%)

Is CD-Induced Short Stature Occult?

Detecting occult CD as a cause of short stature is a function of professional alertness insofar as the clinician considers this condition in a differential diagnosis. Data in the medical literature, as well as from our own experience, show that many CD patients with short stature have a history of diarrhea at an early age and/or have microcytic anemia. Other diagnostic clues that may indicate CD include increased stool fat, antigliadin and antiendomysial antibodies, and low folate and serum ferritin levels.[3-5] In a few cases, however, there may be no clue to CD other than abnormal intestinal mucosa diagnosed by an orally obtained jejunal biopsy.

Pathogenesis of Growth Retardation

The cause of growth failure in children with CD has been the focus of many investigations. Initial studies suggested secondary hypopituitarism might be the basis for the retarded growth.[1,12-14] Subsequent assessments, however, failed to substantiate growth hormone (GH) deficiency in most growth-impaired children with CD. On continued investigation, it became increasingly evident that a gluten-free diet could reverse this complication. This finding further emphasized the importance of adequate and appropriate nutrition in maintaining normal linear growth.

The effect of gluten ingestion on the growth pattern of CD patients is still unresolved. Is growth retardation induced by the effect of the disease on the general nutritional status? That is, does malabsorption lead to malnutrition, which, in turn, leads to a decrease in weight and failure to gain height? Or, in addition, is there a direct effect of gliadin peptides on the GH-secreting apparatus, as well as on other hormones affecting growth, such as somatomedin?

GH and CD

Inadequate response of serum GH levels to insulin stimulation was reported by Hamilton in 1969 in one of five CD patients examined.[1] We have examined the plasma GH levels in response to insulin stimulation in CD patients on a normal gluten diet, in patients on a gluten-free diet, and in normal children of comparable age who served as controls (Figure).[12] The CD children showed a lower GH response, as a group, than the normal controls. Also, serum GH response to insulin stimulation in the CD group consuming a normal gluten diet was significantly lower than in the CD group on the gluten-free diet. Similar results have been reported in other studies.[1,7,13,14]

Somatomedin-C (Sm-C), a GH-dependent growth factor modulated by nutrient status, is variable in CD patients.[15-17] We were unable to find a correlation between serum Sm-C levels in CD children and the diet consumed. As would be expected, some CD patients who had low Sm-C levels while on the normal gluten diet had increased levels while on a gluten-free diet. On the other hand, other patients had normal serum Sm-C levels while consuming a normal gluten diet. Data are accumulating to suggest that Sm-C may be a useful marker of nutritional adequacy in patients with inflammatory bowel disease[18,19] but not in patients with CD.

Enhanced Enteric Losses and Nutritional Dwarfism

Any one or a combination of the nutritional alterations may lead to nutritional dwarfing in CD patients. This may occur even in patients

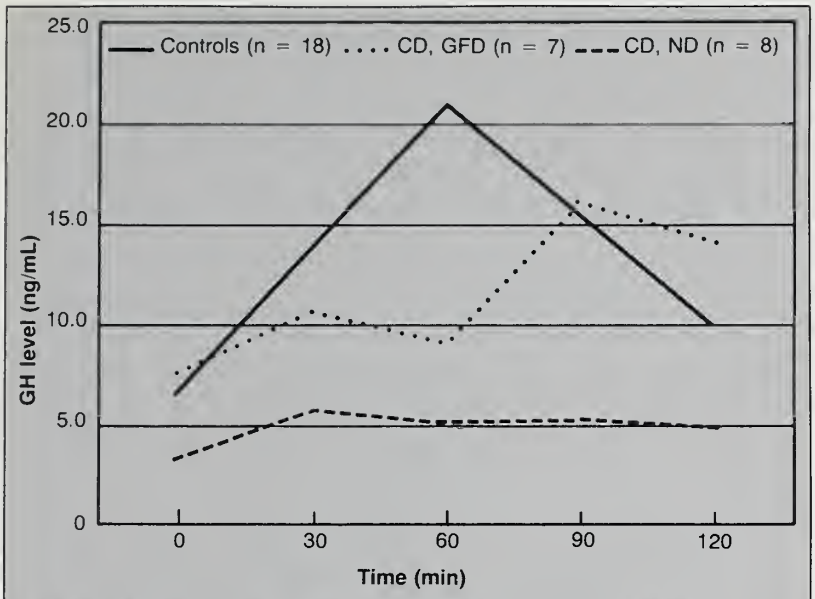

Figure The mean GH responses to insulin are shown for CD patients on a normal gluten diet, CD patients on a gluten-free diet, and normal controls. All were given a standard insulin tolerance test and had an apparent drop in blood glucose levels. At each point, the SD of the GH levels varied from 0.5 to 6.5.

who have an increased body weight/height ratio (i.e., short and plump patients).

The basic defect in CD is destruction of the intestinal epithelial cell layer, with reactive production of intestinal cells up to seven times the normal rate. The net result is flattening of the intestinal mucosa; immature and damaged epithelial cells cover the surface. This blunting of the villi is instrumental in decreasing the absorptive surface of the intestine and producing malabsorption and malnutrition.[3-5] The nutritional status of these patients is further impaired by the defects in the intestinal epithelium that cause protein-losing enteropathy, and is aggravated by the desquamation of the epithelial cells and shedding of lymphocytes. The resultant loss of protein, DNA, and lymphocytes leads to hypoproteinemia and lymphopenia. CD patients also experience intestinal loss of zinc. There is a tendency toward lower serum zinc levels in the CD patients, but these levels are not low enough to produce clinical symptoms.

Children with CD have impaired iron balance as well. Serum ferritin levels in CD patients are often significantly lower than in controls, and a gluten-free diet produces a definite rise toward normal levels. The low ferritin levels reflect impairment of iron absorption, as well as increased iron losses in the desquamating epithelial cells and lymphocytes. Additionally, the serum folate levels are significantly lower in the untreated CD patients and may result from a decrease in the folate absorption caused by the impairment of the deconjugase enzyme present in the brush border of the intestinal epithelial cells. This enzyme facilitates absorption by splitting glutamic acid residues from the folate heptaglutamate in foods and reducing them to mono- or diglutamates. However, it is well known that there is a sevenfold increase of cell turnover and in DNA synthesis in patients with CD. This regenerative effort by the crypt cells in active CD requires folic acid, an essential component of the enzymes involved in the synthesis of DNA. Thus, there is a decrease in folic acid absorption that parallels an increase in folic acid requirements for DNA synthesis in patients with active CD. The net result is decreased serum folate levels.

Diagnosis of CD

Two factors are important to remember when considering occult CD in the differential diagnosis of short stature: 1) Studies show an increased incidence of CD among children hospitalized for examination of short stature; and 2) CD may be present even in the absence of GI symptoms. A small-bowel biopsy, "the gold standard" for the diagnosis of CD, should be performed in all children examined for short stature who show a decrease in the body weight/height ratio, have a history of diarrhea during the first year of life, or present with hematologic abnormalities such as anemia.

Summary

CD is more common than idiopathic GH deficiency as a cause of short stature. Thus, it is important to rule out this disease in children in whom there is no endocrinologic cause of short stature. CD should be suspected in patients who 1) fail to grow at normal rates and have a bone age that is delayed, particularly if by more than 4 years; or 2) have a bone age below that expected for height. Because abnormal absorption may not be detected by common tests even in known CD patients, an intestinal biopsy may be needed for diagnosis. Confirmation of CD as the cause of delayed growth should come from documentation of catch-up growth in weight and height after institution of a gluten-free diet, the only treatment now available for CD.

The original work was supported by a grant from DFG, West Germany.

***Editor's comment**—One of the greatest enigmas in pediatrics today is why celiac disease is so prevalent in Europe and the Middle East (Israel, for example) but not in North America. There are many descendants of Europeans in North America, but the disease is rare. Readers who have a tenable theory, particularly one with supporting data, are encouraged to write to the editors of* Growth, Genetics, and Hormones.

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Even though celiac disease is less frequent in our clinics than in those of Europe, we must remain alert to the possibility that any child with short stature of unexplained etiology may have celiac disease.
Robert M. Blizzard, M.D.

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The Remarkable Catch-up Growth of American Slaves

Richard H. Steckel, Ph.D.
Associate Professor of Economics
Ohio State University
Columbus, Ohio

Editor's Note:
Dr. Steckel is an academic economist whose research relates cultures and environment to growth patterns. He has capitalized on the records kept by slave traders and the U.S. Army during the time of slavery to evaluate the growth of slave children. Examination of those records and a process of logical deduction fuel this fascinating account of how and why slave children grew at the rates they did in the early 19th century. The data and concepts presented will not be used in the clinical practice of medicine, but they do clarify how the children in one culture were exceedingly small until late childhood and then manifested significant catch-up growth. Dr. Steckel presented these data at the International Auxology Conference in England in August 1987, and a longer version of this article appeared in Annals of Human Biology *(1987;14:111-132).*

Robert M. Blizzard, M.D.

Much of our present knowledge of human growth has accumulated by studying healthy children from quasi-experiments created by wartime starvation, poor children who live in developing countries, children who were born with malformations or who otherwise acquired maladies, and from animal experiments appropriately interpreted for parallels with human behavior. The diversity of past cultural and environmental conditions suggests that studies of historical populations may also provide insights into human growth. This article summarizes recent research on the unusual height-by-age profiles of American slaves, a line of work that sheds light on both biological and social processes.

Origins of the Data

Measurements in this study were collected as a by-product of American legislation that, beginning in 1808, prohibited the African slave trade as an import activity, but permitted monitored slave trading to continue along the U.S. coast and inner waterways.[1] Slaves entered the coastal and waterways trade as part of the general westward migration of farming during the 19th century. The law required ship captains who left American ports to prepare duplicate manifests that described each slave by name, age, sex, height, color, and the name of the owner or shipper. The collector at the port of origin retained one manifest, and the captain delivered the other for comparison against the "cargo" by the collector at the port of destination. Thus, the ship captains took measurements as part of an identification scheme designed to prevent smuggling of slaves. The data presented here are based on records of 10,562 manifests housed at the National Archives.[2] A total of 50,606 slaves were involved.

Results

The Table gives the means, mean annual increments, sample sizes, and centiles of modern height standards for males and females in this population. The mean increments fell irregularly from early childhood, then rose during adolescence and reached a peak near age 15 years in males and near age 13 years in females. Before adolescence, boys and girls were about the same height, but earlier maturation propelled the girls beyond the boys at 13 to 14 years. Growth ceased at about age 21 years in men and about age 19 in women.

Young slave children were extraordinarily small, falling near or below the first centile of the Tanner, Whitehouse, and Takaishi standards. Their relative size increased little before age 11, when boys began to exceed the third

Table. Mean, mean annual increment, sample size, and centile of modern standards applied to slave height

Age at last birthday	Males				Females			
	Mean (cm)	Increment	n	Centile	Mean (cm)	Increment	n	Centile
4	91.2	—	195	0.3	91.2	—	206	0.5
5	97.2	6.0	169	0.3	99.0	7.8	200	1.6
6	103.2	6.0	218	0.5	101.6	2.6	262	0.4
7	110.8	7.6	200	1.5	110.0	8.4	241	1.8
8	114.6	3.8	281	0.9	115.5	5.5	337	2.2
9	121.0	6.4	266	1.7	119.6	4.1	306	1.4
10	125.1	4.1	557	1.6	124.6	5.0	528	1.4
11	131.9	6.8	347	3.6	130.4	5.8	443	2.1
12	135.2	3.3	751	2.4	134.8	4.4	736	0.9
13	141.1	5.9	470	3.0	142.0	7.2	556	0.9
14	146.6	5.5	732	2.1	148.0	6.0	765	1.7
15	153.0	6.4	571	1.3	152.4	4.4	812	5.6
16	158.1	5.1	709	1.2	155.5	3.1	1,113	13.3
17	163.2	5.1	655	4.6	157.4	1.9	871	21.5
18	165.7	2.5	1,142	8.9	158.0	0.6	1,268	24.5
19	167.7	2.0	900	14.5	158.6	0.6	594	27.4
20	168.5	0.8	1,527	17.6	158.4	−0.2	1,264	26.8
21	170.5	2.0	944	26.1	158.8	0.4	337	28.4
22	170.2	−0.3	1,374	24.8	159.0	0.2	664	29.5
23	170.6	0.4	795	26.8	158.8	−0.2	404	28.4
24	169.9	−0.7	872	23.6	159.4	0.6	442	31.9
25-49	170.6	0.7	8,725	26.8	159.8	0.4	6,552	34.5

centile and girls, the second centile. The heights then descended through the centiles, primarily because the reference population matured early. But the apparent growth retardation had disappeared and the slaves grew rapidly during and after adolescence. They emerged as adults near the 25th centile (in males) to the 30th centile (in females).

Comparisons

Perspective on the growth profile of American slaves may be obtained in comparisons with poor populations in developing countries and with historical populations. According to worldwide data for the mid-20th century compiled by Eveleth and Tanner,[3] young slaves were among the smallest children ever measured.[3] At age 3, for example, slave children were smaller than children from the urban areas of Bangladesh, who reached the centile of 0.35, and those from the slums of Lagos, Nigeria, who attained centiles of 12.1 as boys and 6.4 as girls at the same age.[4] It is clear that the typical slave child had an exceptionally poor start in life.

The Eveleth and Tanner data also indicated that children and adults of the same population tended to be in similar centiles. If environmental conditions were poor, for example, then both children and adults were correspondingly diminished in stature. This was not true of the slave children whose percentile ratings increased as they matured.

The Figure presents data[5] on populations approximately contemporary with American slaves. The abscissa of the Figure gives average height attained on the eve of adolescence as a percentage of modern standards, whereas the ordinate shows adult stature of the same population relative to modern standards. The heights were estimated from raw data using Preece-Baines Model 1. The first quadrant (NE) depicts populations that were well-off as children and young adults, whereas the third quadrant (SW) shows cases of deprivation in childhood followed by little catch-up growth. Because children and adults in most populations tend to attain similar centiles of modern height standards, one would expect to observe most populations in the first and third quadrants. The American slaves stand out in quadrant 2 (NW) as a case of extensive deprivation in childhood followed by substantial catch-up growth.

Possible Explanations

Ingestion of toxic substances by the mother or young child may cause growth retardation in children. Could excessive alcohol or tobacco consumption have contributed to the small stature of young slaves? These products were available on many southern plantations, but the amounts consumed were probably modest in most cases, as intoxication and frequent breaks for smoking were incompatible with the considerable labor demands of slave agriculture. Moreover, heavy consumption of alcohol or tobacco is inconsistent with the substantial catch-up growth observed among slaves.

The generally high level of mortality and seasonal patterns of deaths tabulated from the records of large southern plantations, along with evidence from feeding patterns and work routines, suggest that nutritional deprivation stunted growth in early childhood.[6] Infant mortality probably occurred at a rate of about 350/1,000, and losses for the age group 1 to 4 were about 201/1,000. Overall, slave losses before age 5 were roughly double those of whites during the period 1830 to 1860. Perhaps two-thirds of the infant deaths involved neonates, and of these approximately three-fourths occurred in the 6 months of February through April and September through November. Stillbirths were concentrated in late autumn and, to a lesser extent, in the period of February through April.

Before the fifth month, pregnant slaves had little or no relief from the arduous work of the preparation and planting season of late winter and early spring and of the harvest of late summer and autumn. In addition, malaria and other fevers

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were common during the "sickly season" of late summer and early autumn. Stillbirths and neonatal deaths often are secondary to deprivation at or near conception, and the neonatal death rate increases with deprivation during the third trimester.[7] This pattern of evidence points to seasonal nutritional deprivation of the fetus, brought on by hard work and, to a lesser extent, by disease.

Poor diet and infections also affected the health of postneonatal slave children. The evidence on breastfeeding practices is scanty, but it suggests that slave infants received breast milk for 9 months to 1 year, whereas white babies continued breastfeeding for more than 1 year. Within 3 months after delivery, the amounts of cotton picked by slave mothers returned to normal levels, and this suggests that one or more daytime breastfeedings may have been eliminated. The substitute diet featured starchy paps and gruels that were often contaminated or served with contaminated utensils. According to owners' records, diarrhea was a common cause of death in slave infants.

Children who survived the hazardous period of infancy subsisted largely on hominy and fat, and their causes of death frequently included diseases aggravated by poor nutrition. In addition, aggregation of children on large plantations probably promoted the spread of communicable diseases, such as whooping cough, measles, and pneumonia.

By ages 8 to 12, work began to place a claim on the slaves' diets, and, other things being equal, the additional physical effort would have retarded growth. Yet it was at these ages that slaves realized some catch-up growth—an indicator that workers were rewarded with good diets, compared with children and other nonworkers. Those in the adult labor force usually received rations of pork (~0.5 lb/day) and other foods, principally corn. In addition, some slaves supplemented their rations with fish, game, poultry, garden vegetables, and other foods. Experienced workers also may have benefited from practice or repetition that reduced their energy expenditure for particular tasks and left more nutrition for growth.

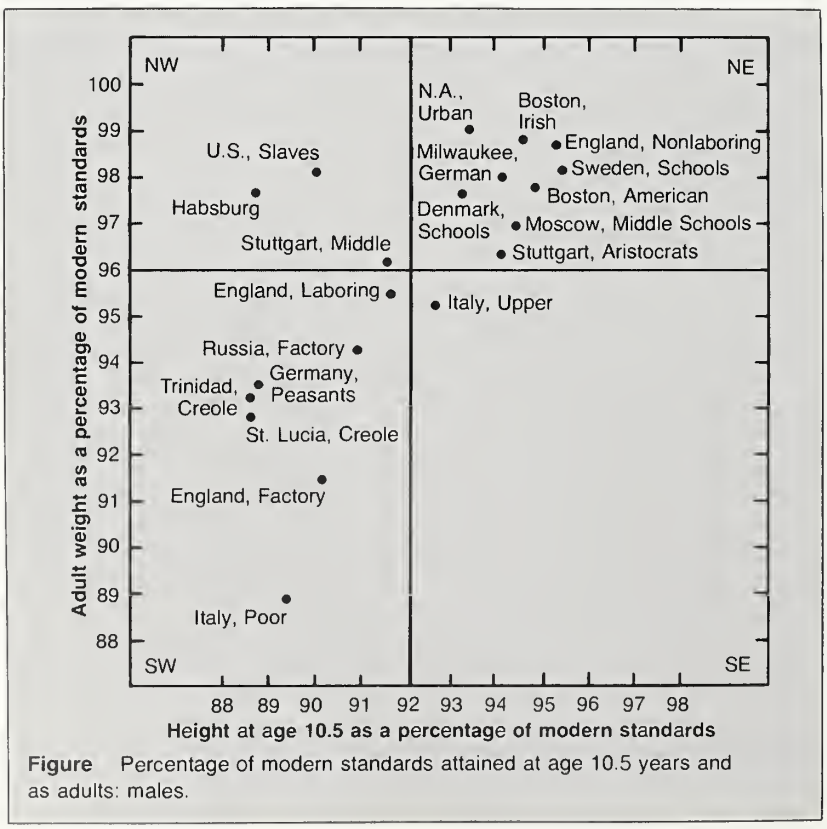

Figure Percentage of modern standards attained at age 10.5 years and as adults: males.

Concluding Remarks

The growth profiles of American slaves suggest that humans have a remarkable capacity for catch-up growth. This finding should be qualified by recognizing that the harsh environment may have eliminated many children who adapted poorly to deprivation. Those who survived to adolescence may have been relatively efficient at utilizing a given level of nutrition for growth.

On the other hand, the chronic nutritional deprivation of young slaves may have stunted mental and emotional development in ways that adversely affected the economic progress of blacks after their emancipation. Most societies that attained near-modern nutritional standards for adults also had children who were relatively well-off. American slaves provide an exception that raises questions about the goals and incentives of resource allocation in free societies, as compared to slave societies. The unusual pattern of food allocation by age may have been achieved partly at the expense of the slave family; for example, workers ate breakfast and lunch in the fields and were probably fed after the young children in the evening, and this left little time for parents to spend with their children on a regular basis.

In summary, data collected for economic purposes may lend itself to analysis and evaluation of scientific parameters.

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Height and Height Velocity

Growth and growth-velocity curves have recently generated considerable interest. Because Dr. James M. Tanner, a member of our Editorial Board, has made significant contributions in this area, we present the following letter and reply. We feel that Growth, Genetics, and Hormones *is an appropriate forum for the exchange of ideas on this critical issue.*

I greeted the Tanner and Davies article[1] enthusiastically. I anticipated that the new longitudinal height-velocity standards would provide definitive data about the normal range of height velocity. I had thought from the earlier work of Tanner and his associates that the lower percentiles on previous height-velocity charts were misleadingly wide because they were based on cross-sectional data and included children whose tempo of puberty was inordinately early or late.

Unfortunately, the Tanner and Davies charts do not solve this problem. For example, examine their longitudinal height-velocity chart for American boys between 8 and 9 years of age: height velocity is 3.75 cm/year at the third percentile and about 3.75-4.0 cm/year for the fifth percentile. Are we then to consider that a linear growth rate of 4.0 cm/year is normal at this age? When one turns attention to the companion longitudinal data for height attained by American boys, one finds that boys in the fifth percentile for late maturers (that is, in the 0.125th percentile) grow from 117 cm at 8 years of age to 121.6 cm at 9 years, a velocity of 4.6 cm/year. Thus, a "normal" growth rate of 4.0 cm/year would cause a child to deviate from the normal growth channel.

These longitudinal standards do not get around the problem that Dr. Tanner had described with cross-sectional standards. Percentiles for velocity necessary to maintain height-channel position ("height-channel velocity") would seem more important in the diagnosis of growth disorders than the percentiles for height velocity since, as Dr. Tanner has taught us, prepubertal children grow to maintain their height-channel position rather than their height-velocity centile position. I would conclude that a height velocity below 4.6 cm between 8 and 9 years of age is subnormal. Why are there these discrepancies? If short-term growth velocities had been used, that would explain the matter because they oscillate about the whole-year channel. However, whole-year velocities were apparently estimated by Tanner and Davies. Their appendix describes the construction of the 50th centile curves for height attained and peak height velocity but not of the outer limits. One cannot calculate growth velocities from the National Center for Health Statistics' curves because all their surveys are cross-sectional (T.A. Drizd, personal communication), so we badly need a more explicit explanation of the Tanner and Davies modeling procedure from which the centiles for height velocity were constructed.

Robert L. Rosenfield, M.D.
Professor of Pediatrics and Medicine
Section Chief, Pediatric Endocrinology
University of Chicago School of Medicine
Chicago, Illinois

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Reply from Drs. Tanner and Healy

Dr. Rosenfield's letter regarding an article one of us coauthored[1] gets us into very deep water. Let us first clear away some misunderstandings. Dr. Rosenfield writes, "I had thought. . . that the lower centiles on previous height-velocity charts were misleadingly wide because they were based on cross-sectional data and included children whose tempo of puberty was inordinately early or late." To this we respond:

1. No velocity centiles were or can be based on cross-sectional data; such a thing is impossible.[2] Dr. Rosenfield presumably means *tempo-conditional data*, which is longitudinal data plotted simply against chronologic age, with variations in tempo leading to early and late puberty being ignored.

2. Such tempo-unconditional velocity centiles do indeed give unpleasantly wide centiles from approximately 8.5 years in boys and 6.5 years in girls in America.[3] If the level of maturity is unknown, the information provided by velocities at these ages is relatively slight.

3. No published velocity standards, whether tempo-conditional or -unconditional, have included "inordinately early or late" maturers so far as we know (if inordinately means that children more than, for example, 2 SD away from the mean for maturity are included in proportions greater than those occurring in the healthy population).

4. Prior to 8.5 years (for convenience, we shall talk about boys only from now on) there is only a small difference between tempo-conditional and tempo-unconditional centiles for velocity. Thus, between 8 and 9 years of age, the 50th centile velocity for 2 SD late maturers is only 0.2 cm/year less, and that for 2 SD

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early maturers only 0.4 cm/year more, than the 5.4 cm/year appropriate to median maturers.

Dr. Rosenfield asks, "Are we to consider that a growth rate of 4.0 cm/year is normal" between 8 and 9 years of age? The answer to this question is straightforward. A velocity as small as this occurs at these ages in about 6% of all healthy boys, in a slightly larger percentage of late maturers, and in a slightly smaller percentage of early maturers. With the usual conventions, it must indeed be regarded as "normal." But, Dr. Rosenfield asks, what if the boy started at age 8 with an attained height at the fifth centile? A velocity of 4.0 cm/year would leave him, at age 9, at a position below his initial centile. Should he be regarded as abnormal?

This question is difficult in unexpected ways.[4] It involves the joint assessment of two pieces of information: the initial height and the velocity. In our case, both are near the conventional lower limit of "normality." However, between 2 years and the beginning of puberty, it is perhaps surprising that the correlation between distance attained and subsequent velocity is very small. This means that our judgment about the velocity *as such* is largely unaffected by its starting point: just about 6% of the subset of healthy boys who are at the fifth centile for height at age 8 will have a velocity as small as 4.0 cm/year over the subsequent year.

Looking at the question another way, the velocity required to keep a boy exactly on the fifth centile between ages 8 and 9 is 4.6 cm/year for a late maturer, and much the same (4.9 cm/year, in fact) for a median maturer. These velocities are around the 20th centile value, and a substantial proportion of healthy boys will have lower velocities. They will fall below their initial "channel" on the distance chart; this is bound to occur with some healthy children, just as some healthy children are bound to fall below the 20th centile at any age. If Dr. Rosenfield were to conclude that a height velocity of 4.6 cm/year between 8 and 9 years of age was abnormal rather than merely "subnormal," then, based on current data, he would be aiming to treat some 20% of the healthy population.

The position is slightly more complicated during puberty, when tempo effects give rise to appreciable correlations between velocities and their starting values. Then the assessment of a velocity needs to take into account its starting value.[5] Regression height standards to make this possible have been published by Cameron,[6] although we are not aware that they have been used in practice. They do provide a practical version of tempo-conditional velocity standards over the pubertal age range where these are potentially useful. As an example, Cameron's figures show that the third centile velocity over ages 14.5 to 15 years is 2.6 cm/year for a median starting height, 2.0 cm/year for those starting 2 SD tall, and 3.1 cm/year for those starting 2 SD short.

Of course, a height at the fifth centile at age 8 years may be regarded as tentative evidence of abnormality and a subsequent yearly velocity of 4.0 cm/year may then be regarded as confirmatory. To assess this, we now need to have the probability in healthy boys of *both* a low starting height *and* a low velocity; thanks to the absence of correlation, this can be calculated as $0.05^2 = 0.0025$, a highly unlikely occurrence in healthy boys as a whole. Notice, though, that the probability of a height and a velocity both below the 15th centiles(two not very unlikely events in themselves) is only 0.02. Notice also that if we label as abnormal any boy with a height *or* a velocity below the third centile, we shall wrongly label not 3% but nearly 6% of the healthy population. This might suggest that the "normal" limit should be set at, for example, the 1.7th centile to get back to an overall false-positive rate of 3%. This in turn would prevent us from detecting some truly abnormal children from their low starting height, and our false-negative rate would be increased. We have explored elsewhere[7] some possible ways of assessing two or more successive measurements in terms of the false-positive and false-negative rates of different tactics. We might, for example, declare as abnormal those boys with a starting height below the third centile, or those with both starting height and subsequent velocity below the 10th centile.

Finally, we answer the query in Dr. Rosenfield's last sentence. Briefly, to obtain velocity centiles, Tanner and Davies[1] followed the methods of Tanner, Whitehouse, and Takaishi.[3] Instead of British data, however, we used data from the Harvard School of Public Health and the Berkeley Growth Study. Individuals were lined up on their peak height velocity ages, and the SD was calculated for the preceding year, the year before that, etc. This led to an estimate of the SD of velocity for chronologic age for a given tempo cohort. Prior to puberty, the SD of whole-year velocities was estimated from the data straightforwardly. The junction of the prepubertal and pu-

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bertal SD lines was smoothed graphically (a minor adjustment). Centiles were then calculated, assuming (after test) a Gaussian distribution of velocities within tempo cohort.

We find that we encounter new theoretical problems each time we consider the best way to use velocity standards. We hope that others will add their views on this subject.

J.M Tanner, M.D., D. Sc.
M.J.R. Healy, M.D.

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Letter to the Editor

I am writing in reference to your editorial comments (*Growth, Genetics, and Hormones*, Volume 4, Number 2) on our article, "Short-Term Testosterone Treatment at Bone Age 12-13 Years Does Not Reduce Adult Height in Boys with Constitutional Delay of Growth and Adolescence," by Zachmann M, Studer S, and Prader A (*Helv Paediatr Acta* 1987;42:21). You rightly pointed out the need for caution in interpreting mean data for groups when the individual results are not known.

Our article was a short version of a more detailed doctoral dissertation that was written by Dr. Studer under my guidance. In the abridged version, only mean values for groups were shown, to save space. In the original dissertation, however, there were three figures indicating each individual difference between predicted height (according to Bayley-Pinneau; Roche, Wainer, and Thissen; and Tanner et al) and the adult height actually reached. These figures showed that the differences are equally distributed among plus (ie, adult height greater than predicted) and minus (ie, adult height less than predicted), and that a few individual cases did not unduly influence the mean values. A copy of the dissertation is available to interested readers free of charge; keep in mind that it is written in German.

As far as the testosterone dose is concerned, it should be noted that ours was a retrospective study and that some of the patients were receiving doses higher than what is today considered appropriate. Our present policy is to administer 50-100 mg of long-acting testosterone esters for a period of 6 months, when bone age has reached a value of 12.5 years or more. It is thus similar to the policy stated in your comment. In contrast, we do not treat younger boys with oxandrolone. In view of the recent characterization of one single androgen receptor, there seems to be no evidence that the action of oxandrolone or other synthetic androgens might be different in any way from that of testosterone itself. Testosterone offers advantages of degradation (peripheral aromatization and glucuronide esterification), so it might be more physiologically appropriate to treat younger boys with extremely low doses of testosterone (eg, 5-10 mg of a long-acting preparation every 2 weeks). This dosage, however, will require further short-term metabolic and long-term treatment studies.

Milo Zachmann, M.D.
Professor of Pediatric Endocrinology
Department of Pediatrics
University of Zürich
Kinderspital, Zürich
Switzerland

Dr. Blizzard's reply

The data in Dr. Zachmann's article (Helv Paediatr Acta *1987;42:21) and those in other recent reports indicate that low-dose depot testosterone (50-100 mg IM each month for 6 months), in boys with constitutional delay of growth and adolescence (CDGA) who have a bone age* $\geq$ *12.5 years, generally does not decrease ultimate height. Dr. Zachmann adequately responded to my constructive questions regarding the data that could not be presented in the* Helvetica *article, and I am pleased to see this response.*

In my editorial comment on Dr. Zachmann's article I suggested that oxandrolone might be preferable for young patients. Dr. Zachmann legitimately questions whether oxandrolone has any advantages over testosterone at very low doses in boys who have CDGA and a bone age $<$ *12.5 years. His argument that oxandrolone and testosterone should act similarly because only one androgen receptor has been identified is logical and very possibly correct. Confirmation of this argument, however, will require specific studies comparing the effects of testosterone at very low doses (5-10 mg every 2 weeks IM) with the usual doses of oxandrolone (0.1 mg/kg body weight every day) on nitrogen retention, growth acceleration, and virilization. Until such studies are accomplished, I am unprepared to say more than, "Possibly, Dr. Zachmann is correct."*

EDITORIAL COMMENT

Slow Grows the Child: Psychosocial Aspects of Growth Delay

Edited by Bryan Stabler, Ph.D., and Louis B. Underwood, M.D.
Published by Lawrence Erlbaum Associates, Hillsdale, New Jersey, 1986

Slow Grows the Child is a very readable and important book. It compiles for the first time information concerning the psychosocial aspects of short stature, a condition to which many physicians do not often pay close attention. It will also serve as a primary reference for those interested in performing the needed prospective longitudinal studies of cognition, achievement, psychosocial functioning, and other developmental and behavioral factors in short children.

This short volume (less than 200 pages) includes 14 papers that were presented at a 1984 symposium on the psychosocial aspects of growth delay held in Washington, D.C. A report based on that conference appeared in a previous issue of this publication (Vol. 1, No. 1). The book reviewed here is an excellent source for those who were unable to attend that symposium.

The value of the book is enhanced by the logical sequence of its chapters. In the first, Holmes et al describe the longitudinal evaluation of behavioral patterns in children with short stature and conclude that there is an age-related decline in the ability to adjust during early adolescence. In the next chapter, Richman et al discuss academic and emotional difficulties of children with constitutional delay of growth and describe how these children, who are often socially withdrawn and aloof, internalize emotional concerns. In the third chapter, Young-Hyman considers the social competence of children with growth hormone (GH) deficiency, constitutional delay of growth, and genetic short stature. The author concludes that short stature per se does not represent a handicapping condition, but the age of onset and the perceived and real growth delay are critical factors affecting social competence.

The next series of chapters concerns children with GH deficiency and their academic and emotional functioning. Drs. Siegel and Hopwood report that children with hypopituitarism have overall average intelligence but show significant variability on cognitive testing and difficulty with visual-motor integration. Three chapters, by Dean et al, Clopper et al, and Mitchell et al, deal with the long-term psychosocial follow-up of children treated with GH. The results presented in these chapters, however, are often at variance with each other. For example, an 8% unemployment rate is described in one chapter while a 35% unemployment rate is described in another. Both of these chapters state that approximately 25% to 35% of the individuals queried are now living independently. Other findings are that only 58% of GH-deficient adults have a driver's license, and 85% have never married. Although the majority (85%) of subjects in one study stated that short stature was not a serious problem, another study found that subjects had poor self-perception and 38% had sought psychological counseling.

Two chapters deal with cognitive and psychological studies in girls with Turner syndrome. As expected, visual-spatial problems were identified, but neuropsychological dysfunction appears to be even more prevalent. When one compares adults with Turner syndrome with adult women who have constitutional short stature, one finds that there are an equal number of major depressive episodes in both groups and no difference in the incidence or extent of psychological impairment.

A chapter by Drs. Wilson, Duncan, Dombusch, Ritter, and Rosenfeld looks at the effects of growth

Meet the Editorial Board

Associate Editor
William A. Horton, M.D.

Dr. Horton is Professor of Pediatrics and Medicine, Director of the Division of Medical Genetics, and Director of the Chondrodysplasia Laboratory at the University of Texas Health Science Center in Houston.

Dr. Horton received his bachelor's degree with honors in zoology from the University of Kansas and earned his medical degree in 1971 from the University of Kansas School of Medicine, where he received the Walter F. Sutton Award in Human Genetics and was elected to Alpha Omega Alpha. After completing his internship and residency at Kansas University Medical Center, he worked as a staff associate at the National Institutes of Health (NIH) and as a fellow in medical genetics under Dr. David L. Rimoin at Harbor-UCLA General Hospital, Los Angeles. Dr. Horton joined the faculty of the University of Texas in 1983.

Dr. Horton is a member of the Board of Directors and is Chairman of the Research Committee of the Human Growth Foundation. The author of more than 120 articles on the chondrodysplasias, he chaired the NIH Conference on the Biological Basis of Human Chondrodysplasias, held in September 1987. Dr. Horton is a fellow of the American College of Physicians and a member of the American Society of Human Genetics, the American Federation of Clinical Research, and the Society for Pediatric Research.

on intellectual function and describes an association between height and IQ scores. A retrospective study of children with emotionally based failure to thrive suggests that an early onset of chronic failure to thrive has a poor prognostic outcome; ultimately, these children exhibit poor attachment to their parents. A chapter on environment and intelligence suggests that manipulating the environment of children with psychosocial short stature can prevent permanent retardation and that significant intellectual catch-up growth can occur even if the child is not rescued until early adolescence. Finally, there is a chapter on the ambivalence involved in parenting short-statured children.

Included in this volume is an address by Dr. Leonard P. Sawisch of the Michigan Department of Education, the keynote speaker at the symposium. Dr. Sawisch, who is 4′ 4″ tall, reviews the psychosocial aspects of short stature from his perspective. He describes his perception of himself as a short adult, and how short adults in general perceive the way society views them. The presentation is amusing and anecdotal but disappointing in terms of how we, as a society, have affected the lives of our children and others with handicaps.

Although there are limitations in a number of the studies described in the book—some included small groups of subjects, some were performed retrospectively, some had diverse methods of evaluation, and some grouped together many discrete syndromes involving short stature—this book should nevertheless be on the required reading list of all who treat short children. Those interested in more information on psychosocial aspects of short stature are also referred to "The Disability of Short Stature," a recent paper by C.M. Law (*Arch Dis Child* 1988;62:855-859). Law carefully reviews many of the topics presented in depth in *Slow Grows the Child.*

William L. Clarke, M.D.

Abstracts From the Literature

Decreased Height Velocity in Children and Adolescent Boys Before the Diagnosis of Crohn's Disease

To assess the prodromal growth patterns of Crohn's disease patients, sequential growth data and height and weight velocities were studied in 50 white children and prepubescent adolescents (31 boys, 19 girls) with Crohn's disease. Height and weight velocities of the patients were compared by calculating the SD score (*z* score). Inclusion criteria were at least four separate height recordings between the age of 4 years and the onset of symptoms attributable to Crohn's disease, premorbid height ≥ fifth percentile, Tanner stage no greater than II, and absence of other chronic medical conditions. A decrease in height velocity was defined as a sustained decline of 25% from the premorbid height velocity or to the third percentile for height velocity.

Three distinct patterns of linear growth emerged in this patient population. Forty-six percent (23 patients) had a decrease in height velocity between 4 and 72 months (median, 12 months) before the onset of symptoms attributable to Crohn's disease. Forty-two percent (21 patients) had a decrease in height velocity after symptoms had developed but before Crohn's disease had been diagnosed. Twelve percent (six patients) sustained a normal height velocity until Crohn's disease was diagnosed. There were no differences in the site of gastrointestinal involvement and symptoms between the patients who showed a decrease in height velocity and those who did not. Although the majority of patients with growth failure demonstrated poor weight gain, a subset (22%) had decreased linear growth while maintaining a normal weight velocity. Of the six patients with normal linear growth, five continued to maintain normal weight gain.

Kanof ME, Lake AM, Bayless TM. *Gastroenterology* 1988;95: 1523-1527.

Editor's comment—*This interesting study reports on the pattern of growth of patients with Crohn's disease before presentation of symptoms and diagnosis. It illustrates a pattern of nutritional dwarfing in which cessation of body weight progression usually precedes height deceleration. It also shows that a body weight/height deficit is not always present in patients with Crohn's disease. Nutritional dwarfing has been reported in patients who are overweight for their height; the best example, studied by Dietz and Hartung (*Am J Dis Child *1985;139:704-708), is obese children given hypocaloric diets who fail to grow in height. Trowbridge and co-workers reported that this occurs in other malnourished populations as well (*Am J Clin Nutr *1987;46:411-418). My colleagues and I have observed similar patterns of growth in children with atypical eating disorders leading to nutritional dwarfing who have no body weight/height deficits, but show a lack of weight progression (*Semin Adolesc Med *1987;3:255-266). Nutritional alterations other than caloric or protein deficits may account for nutritional dwarfing without deceleration in weight velocity. For example, low blood zinc levels might precede both the onset of the symptoms and the diagnosis of inflammatory bowel disease (Lifshitz F, Nishi Y. In: Anast C, DeLuca H [eds]:* Pediatric Diseases Related to Calcium. *Elsevier, 1980). Unfortunately, this study did not address the possible etiopathogenesis of the different growth patterns among these patients.*

Fima Lifshitz, M.D.

Birth Weight and Childhood Growth

Previous studies have recorded that low birth-weight (BWt) infants often exhibit rapid growth in infancy, but do not achieve the same weights and heights in childhood as do their counterparts with normal BWt. Furthermore, low BWt term infants do not grow as well as preterm low BWt infants after the first months of life, indicating the negative effect of intrauterine growth retardation (IUGR) on later growth.

In this report, the relationship between BWt and later childhood growth was studied in several thousand infants. The infants were divided into eight BWt categories, beginning with a BWt of 1,000 g and extending, in 500-g increments, to 5,000 g. *Z* scores of height for age (H/A), weight for age (W/A), and weight for height (W/H) were calculated. These *z* scores represent the distance of the observed value from the median of the age-specific and sex-specific reference curve, expressed in SD units. All children were observed from birth to 60 months of age. To evaluate the possible role of BWt in subsequent childhood obesity, the investigators calculated the percentage of children in each BWt category who had W/H *z* scores > 2.0.

The effect of low, intermediate, and high BWt on growth persisted during the 60 months, although the marked discrepancies in mean weight for the eight groups at birth (mean *z* score, −2 to +2) were less discrepant than those observed at 60 months of age (mean *z* score, −1 to +1). Each group continued in its own growth channel in relationship to the other groups, and, therefore, the infants born weighing between 1,000 and 1,500 g were the most weight-retarded at 60 months, whereas the infants with BWt values of 4,500 to 5,000 g were the most weight-accelerated.

The relationship between BWt and *z* scores for H/A were relatively constant after the 24th month. As BWt increased, the percentage of children who had a *z* score < 2.0 for height at 36 to 41 months declined considerably. However, 12.3% of the very low BWt infants continued to have a *z* score < 2.0, as compared with 2.3% of those with a BWt of 3,500 to 4,000 g and only 0.5% of those with a BWt of 4,500 to 5,000 g (Table). The W/A and W/H spread is also presented in the Table.

The authors compared the growth of preterm and term infants weighing 2,000 to 2,499 g at birth (Figure). H/A at 0 to 2 months was similar in both groups. Later, the

Table. Prevalence of abnormal growth by birth weight for children 36 to 41 months of age in the Tennessee Women, Infants, and Children Program, 1975 to 1985

BWt category (g)	H/A < −2.0 *z* (%)	W/A < −2.0 *z* (%)	W/H < −2.0 *z* (%)	W/H > −2.0 *z* (%)
1,000-1,499	12.3	19.8	5.6	1.0
1,500-1,999	11.0	10.4	4.5	1.0
2,000-2,499	11.3	10.6	2.9	1.9
2,500-2,999	7.4	5.9	1.3	2.1
3,000-3,499	4.2	2.9	0.9	2.4
3,500-3,999	2.3	0.9	0.4	3.7
4,000-4,499	1.3	0.5	0.4	5.0
4,500-4,999	0.5	0.0	0.0	8.7

BWt = birth weight; H/A = height for age; W/A = weight for age; W/H = weight for height.

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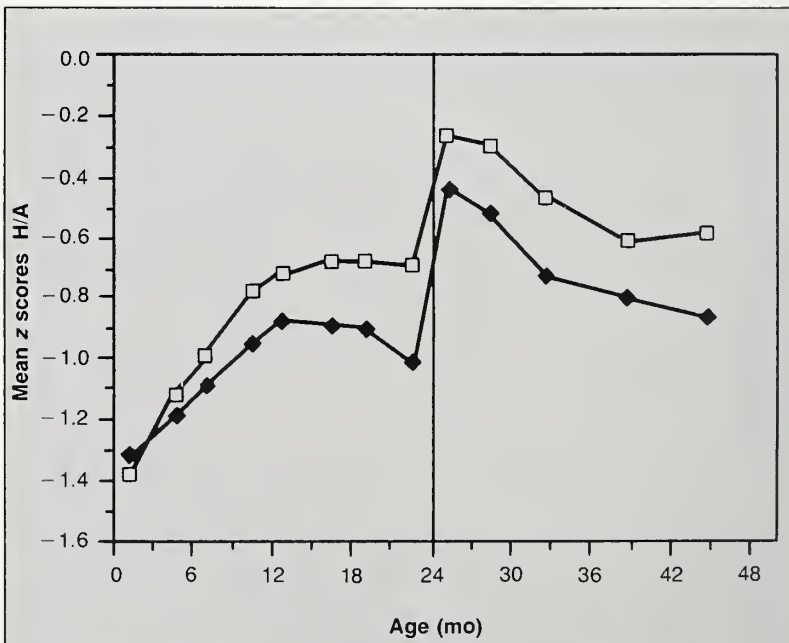

Figure Mean H/A *z* scores for intrauterine growth-retarded (◆) *v* premature (□) infants 2,000 to 2,499 g by 3-month age groupings for children < 36 months of age and 6-month groupings for children 36 to 47 months of age. Based on Tennessee-Linked Special Supplemental Food Program for Women, Infants, and Children and birth certificate records, 1975 to 1985.

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IUGR infants had lower *z* scores than did the premature infants with the same BWt. Median *z* scores in both premature infants and infants with IUGR remained considerably less than normal, however. Mean *z* scores for all parameters differed by 0.2 to −0.3 between the two groups, with the preterm infants being taller and heavier than the IUGR group.

High BWt appeared to be a risk factor for obesity (Table). The very high BWt group included 8.7% of the infants with *z* scores >-2.0 (W/H).

The authors concluded that BWt strongly predicts future growth in early childhood. Although low BWt infants exhibit significant weight gain in the first 12 months, they are likely to remain shorter and lighter in early childhood than children with higher BWt. Conversely, infants with higher BWt remain taller and heavier on average, and increased BWt is associated with a substantial increase in prevalence of childhood obesity. Finally, IUGR is a stronger risk factor than prematurity for short stature and low weight. Preterm children of the same BWt sustain less permanent growth impairment over the 60 months of observation than those who have IUGR, although both groups remain smaller than their normal BWt counterparts.

Binkin NJ, Yip R, Fleshood L, et al. *Pediatrics* 1988;82:828.

Editor's comment—*This report provides important data to assist in predicting the height and weight at 5 years of age in infants of various sizes. The authors are to be commended for a study that was both much needed and precisely conducted.*

Robert M. Blizzard, M.D.

Natural History of Williams' Syndrome: Physical Characteristics

Williams' syndrome is a relatively common, sporadic condition marked by short stature, developmental disability, a characteristic craniofacial appearance, characteristic behavior, frequent failure to thrive in the newborn period, typical cardiac lesion (supravalvular aortic stenosis), and, occasionally, hypercalcemia. Most pediatricians feel that they can recognize the syndrome because of the typical elfin facies. Before this excellent study was conducted, however, the natural history of Williams' syndrome through adulthood, its medical complications, and its progressive nature had not been defined. Morris and colleagues collected information from multiple sources in Utah and Kentucky and from the Williams' Syndrome National Association. Evaluations varied from extensive, on an outpatient basis over a 2-day period, to a format of questionnaires answered by the subjects' parents. A total of 109 subjects were included in the study.

The intelligence of the study subjects varied widely, from severe mental retardation to normal (IQ range, 20 to 106), but most subjects had relative verbal and expressive strengths. Auditory input was much better than visual and motor integration. Distractibility and attention deficits were common, occurring in 84% of subjects. Other frequent problems were esotropia (50%) and hyperopia. Eighty-five percent exhibited a unique hypersensitivity (hyperexaggerated startle) to sudden, loud sounds.

Most individuals had hoarse voices, irrespective of documented hypercalcemia. Most had small, widely-spaced teeth with malocclusions and hypoplastic enamel.

Seventy-nine percent of all subjects had cardiac murmurs, but only 18% required cardiac surgery. Enuresis and constipation were frequent. Joint contractures were progressive. Initial joint laxity was followed by progressive limitation. Toe-walking, stiff and awkward gait, and lordosis occurred regularly; sequelae related to hypercalcemia, such as renal, intracranial, and abdominal aortic calcifications, also occurred regularly.

Most adults with Williams' syndrome were not able to live independently and had multiple chronic medical problems.

Morris CA, Demsey SA, Leonard CO, et al. *J Pediatr* 1988;113: 318-326.

Editor's comment—*This is an extremely important paper—essential for any physician caring for an individual with Williams' syndrome.*

Judith G. Hall, M.D.

Malformation due to Presumed Spontaneous Mutations in Newborn Infants

An estimate of the frequency of new mutations and the mutation rate among congenital anomalies has been made through an ongoing study of newborns. Congenital anomalies among live-born and stillborn infants of at least 20 weeks' gestation were tabulated over a 10-year period at one institution. Of 69,277 infants, 1,549 (2.24%) had some type of congenital anomaly. Anomalies suggestive of single-gene disorders were found in 48 of 69,277 infants (0.07%). Family studies suggested that 11 of these 48 single-gene disorders represented new mutations: 10 were autosomal dominant and one was X-linked. The reported mutation rate, 11 of 69,227 (0.00016), was lower than rates quoted in similar studies. There were no differences in the ages of the female or male parents of the infants with mutations when compared with controls. The spontaneous rate for achondroplasia was 1.4/100,000

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Mutations in Newborn Infants

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births; the Apert syndrome occurred with the same frequency. The rate was 0.7/100,000 births for the Adams-Oliver, Freeman Sheldon, Hold Oram, Osteogenesis Imperfecta II, and spondylo-epiphyseal dysplasia congenital syndromes. As in many other studies, skeletal and limb anomalies are most easily recognized in newborns and, therefore, useful in estimating new mutation rates.

The causes of the congenital anomalies could be established in approximately half the cases, thanks to careful evaluation and follow-up (Table).

These findings emphasize the possibility that malformations caused by a single mutant gene occur unexpectedly among many infants born to healthy parents. There was no family history in 10 of the 21 infants (48%) with autosomal dominant disorders, in 5 of the 10 infants (50%) with autosomal recessive disorders, and in 1 of the 5 infants (20%) with X-linked disorders. The authors found it useful to address this issue in genetic counseling, because parents often assume that the absence of a history of an affected family member rules out the possibility of a genetic cause.

Table. Causes of congenital abnormalities

	No. of infants (n = 1,549)	Percentage of infants
Genetic		
Chromosomal abnormalities	157	10.1
Single mutant gene	48	3.1
Familial single gene	225	14.5
Multifactorial	356	23.0
Teratogen	49	3.2
Uterine factor	39	2.5
Twinning	6	0.4
Unknown	669	43.2

Nelson K, Holmes LB. *N Engl J Med* 1989;320:19-23.

Editor's comment—*This study is important, for both establishment of baseline data and as an ongoing monitor of possible increasing rates. It is of interest that the mutation rates seem to be lower than those frequently quoted in the past. The authors' term "malformations" is something of a misnomer, because many of the anomalies described are deformations or disruptions. The generic term congenital anomaly is preferred, unless a true malformation (ie, failure of normal formation) has occurred.*

Judith G. Hall, M.D.

Physiological Growth Hormone Secretion During the Recovery from Psychosocial Dwarfism: A Case Report

Stanhope and colleagues reported on 18-hour growth hormone (GH) profiles, sampled every 15 minutes from 1300 hours to 0800 hours, in a 6-year, 4-month-old boy with psychosocial dwarfism. On admission to the hospital, this boy had a height SD score of −3.3 and an inadequate GH response to insulin hypoglycemia (maximum, 1.8 μg/L). Three GH profiles were performed: on admission, after 6 days, and at 18 days. During the initial profile, peak GH was greater during the day than overnight. After admission, there was a progressive increase in GH secretion, with maximum GH peaks occurring during early sleep. The increase in GH secretion was achieved by an increase in pulse amplitude without alteration of pulse frequency. Peak GH secretion during sleep rose from 8.2 μg/L on admission to 17.5 μg/L on day 6, and to 25.0 μg/L on day 18. The pattern of GH pulsatility and peak GH achieved at the onset of sleep was consistent with data previously collected in normal children.

Stanhope R, Adlard P, Hamill G, et al. *Clin Endocrinol* 1988;28: 335-339.

Editor's comment—*Pharmacologic tests of growth hormone (GH) secretion have demonstrated that the GH deficiency in psychosocial dwarfism is reversible. The present report demonstrates the pattern of that reversibility and corroborates the findings of earlier studies with pharmacologic stimuli. Although this is only a single case, the findings are very important. It would be interesting to study GH release in response to growth hormone-releasing hormone in these children.*

William L. Clarke, M.D.

In Future Issues

The Morbid and Functional Anatomy of the Human Chromosome Map in Endocrine Disorders and Hormonal Genes
by Victor A. McKusick, M.D.

Assessment and Management of the Psychological Aspects of Short Stature
by Heino Meyer-Bahlburg, Ph.D.

Gonadotropin and Steroid Concentrations in the Fetus and Newborn
by Claude Migeon, M.D.

Growth in Late Adolescence
by Alex Roche, M.D.

Oestrogen Treatment of Constitutionally Tall Girls with 0.1 mg/day Ethinyl Oestradiol

Thirty-five constitutionally tall girls (mean age, 12.5 years) were treated with ethinyl estradiol, in a dosage of only 0.1 mg/day. Their ultimate heights were compared with those of 23 untreated girls of similar initial ages, bone ages (BAs), and predicted adult heights, and with those of five girls treated with ethinyl estradiol, 0.3 mg/day. Treatment lasted more than 2 years for the girls whose BA was > 12.5. Final heights were defined as heights measured at the end of a year during which growth was < 0.7 cm.

The Bayley-Pinneau predictions underestimated by an average of 0.7 cm the heights of controls whose BA was <12.5 years, and overestimated by 0.6 cm the heights of controls with a BA > 12.5 years. Making allowance for these discrepancies, the investigators calculated that the reductions in predicted adult height achieved by estrogen treatment averaged 7.4 cm in girls with BA values > 12.5 years. The authors concluded that the higher dosage of estrogen offers little, if any advantage over the dosage of 0.1 mg/day.

Bartsch O, Weschke B, Weber B. *Eur J Pediatr* 1988;147:59.

Editor's comment—*The authors admit that it is difficult to compare their results with those in the literature because of methodological differences in determining BA and predicting height. Nonetheless, it certainly seems that the lower, and hence more desirable, dosage of estrogen produces much the same results as the higher one. The authors' review of results in the literature is also a valuable one.*

James M. Tanner, M.D., D.Sc.

Changes in Serum Insulin Concentration During Puberty and Their Relationship to Growth Hormone

Hindmarsh and colleagues investigated the relationship between insulin concentration and growth hormone (GH) secretion during puberty in a cohort of 40 tall or short children. Oral glucose tolerance tests were performed in 34 children during puberty and in six adolescents who had reached their final height. The pubertal children were growing at a normal velocity for their stage of development and had no family history of insulin-dependent diabetes. Following glucose ingestion, blood samples were drawn at time 0, and at 30-minute intervals for 3 hours. In addition, 24-hour GH profiles were determined in 16 tall girls (four prepubertal, six in early puberty at breast stages II and III, and six in late puberty, at breast stages IV and V). Twenty-four-hour GH (sampled every 20 minutes) and insulin profiles were obtained in 13 of the 40 children (five short prepubertal, four tall prepubertal, and four tall pubertal). GH pulses were identified, and incremental areas under the glucose and insulin curves were calculated.

The 34 children and six young adults demonstrated no significant increase in fasting blood glucose or in incremental area under the glucose curve. In both tall and short pubertal children there was a significant increase in fasting insulin concentration during puberty; this increase was related to pubertal status rather than stature. The incremental area under the insulin curve increased almost twofold. Age played no part in these changes. Among the six young adults, the glucose and insulin parameters resembled those of prepubertal children. Among individuals in whom GH secretion was studied, increases in fasting insulin were seen at breast stages II and III, and declines were seen at breast stages IV and V. The changes in GH pulse amplitude were coincident with the changes in fasting insulin concentration. There was a threefold increase in the mean sum of GH pulse amplitudes between prepubertal children and girls at breast stages II and III.

The authors concluded that they have demonstrated a threefold increase in serum insulin concentration during puberty and that this increase is coincident with the rise in GH associated with breast development stages II and III. They suggested that during pubertal growth in children with diabetes, the standard dose of insulin should be doubled and possibly tripled to maintain good metabolic control and maximize pubertal growth. As further evidence that the changes in insulin secretion are due to GH, they cited the increase in fasting insulin concentrations in 14 prepubertal children during the first year of exogenous GH therapy.

Hindmarsh P, Di Silvio L, Pringle PJ, et al. *Clin Endocrinol (Oxf)* 1988;28:381-388.

Editor's comment—*Amiel and colleagues (*N Engl J Med *1986;315:215) have previously demonstrated impaired insulin action in pubertal children with diabetes and in their nondiabetic siblings. As Hindmarsh et al point out, the comparison with siblings of children with diabetes may not be appropriate, and clamp studies such as those performed by Amiel et al may not be as physiologically meaningful as the oral glucose loads given in this most recent study. Although this investigation studied children at a variety of prepubertal and pubertal phases, including differences of stature, its findings are significant and suggest one of the reasons for poor glucose control in adolescents with diabetes. Longitudinal studies are needed to corroborate these findings.*

William L. Clarke, M.D.

MEETING CALENDAR

July 9-12 Clinical Genetics Conference on Clinical Applications of Molecular Genetics. Lafayette Hotel, 1 Avenue de Lafayette, Boston, MA. Contact: Sue Greene, March of Dimes, 1275 Mamaroneck Avenue, White Plains, NY 10605 (914-997-4524)

September 23-25 30th Annual Meeting of the American College of Nutrition. Omni International Hotel, Norfolk, Virginia. Contact: Kay Balun, Administrative Assistant, American College of Nutrition, 345 Central Avenue, Suite 207, Scarsdale, NY 10543 (914-723-4247)

October 11-14 41st Annual Postgraduate Assembly of The Endocrine Society. Fairmont Hotel, New Orleans, Louisiana. Contact: The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

October 29-November 3 Joint Meeting of the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology (scientific sessions, October 30-November 1). Jerusalem Hilton, Jerusalem, Israel. Contact: Zvi Laron, M.D., Beilinson Medical Center, Petah Tikva 49 100 Israel

November 12-15 The Annual Meeting of The American Society of Human Genetics, Convention Center, Baltimore, Maryland. Contact: Jean Francese, American Society of Human Genetics, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1825)

Address for Correspondence
Please send all correspondence to Robert M. Blizzard, M.D.
Department of Pediatrics
University of Virginia
School of Medicine
Charlottesville, VA 22908.

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Robert M. Blizzard, M.D.
c/o McGraw-Hill Healthcare Group
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Mapping the Genes for Hormones and Growth Factors and the Mutations Causing Disorders of Growth

Victor A. McKusick, M.D.
University Professor
Department of Medical Genetics
Johns Hopkins University School of Medicine
Baltimore, Maryland

In 1968, a Johns Hopkins Ph.D. candidate named Roger Donahue found linkage between the Duffy blood group gene and a particular heteromorphism of chromosome 1.[1] His report marked the first "mapping" of a specific gene to a specific autosomal location. Already by that time, 68 genes had been assigned with some confidence to the X chromosome, mostly via observations on the typical pedigree patterns of "sex-linked" inheritance. These 68 established X-linked traits, along with other, less certain linkages, were cataloged in the second edition of my book, *Mendelian Inheritance in Man*,[2] published in 1968.

In the remarkable decades since Donahue's report, specific genes have been assigned to specific chromosomes and chromosome regions at an ever-accelerating pace. The totals are now more than 150 genes assigned to the X chromosome and more than 1,300 assigned to specific autosomes. At least some regional information is available for more than half of the genes on the X chromosome and for more than 80% of the autosomal loci—ie, not only the chromosome for these genes is known but also, with fair precision, where on the chromosome each resides.

Methods for Mapping

The rapid advances in this field can be credited to the development of new methods, specifically, the commingling of four methodologic streams: family linkage studies, chromosome studies, somatic-cell hybridization studies, and molecular genetic studies. The latter two methods in particular have been largely responsible for the accelerated pace of discovery in recent years (Figure 1).

The early 1970s saw the introduction of somatic-cell hybridization, which correlates chromosome studies with the segregation of human cellular characteristics in subclones from rodent-human cell hybrids. As indicated in Table 1, somatic-cell hybridization in all of its variations has been responsible for the largest number of assignments of genes to autosomes.

Beginning about 1980, molecular genetic methods entered the methodologic mix. Southern blot analysis of DNA from somatic hybrid cells permitted the mapping of human genes, even though they are not expressed in the cultured cells. Recombinant DNA restriction enzyme technology provided DNA markers (restriction fragment length polymorphisms, or RFLPs, pronounced "riflips") for use in family studies. Molecular genetics also provided the methods for in situ chromosomal hybridization, a combination of molecular genetic and chromosomal studies.

It is of considerable interest that in situ hybridization has risen to second place in the production of autosomal assignments (Table 1), because the methods for reliable in situ hybridization for mapping of single-copy genes did not become available until 1981. The first gene assigned a chromosomal location by in situ hybridization was that encoding the kappa light chain of immunoglobulin, mapped by Ferguson-Smith and colleagues in 1981. Also in that year, Harper and colleagues[3] used in situ hybridization to confirm the assignment of the insulin gene to chromosome 11 and to narrow the localization to the tip of the short arm of that chromosome.

In This Issue

Today, as soon as a gene is cloned it is standard procedure to determine the chromosome that carries it by hybridization of the gene probe to DNA from a panel of rodent-human somatic-cell hybrids, and then to corroborate the chromosomal assignment and regionalize it by in situ hybridization. In the case of a gene that has not been cloned, other methods may be required. If the normal ("wild-type") gene is expressed biochemically, immunologically, or in other ways at the cellular level, it may be possible to map it by somatic-cell hybridization. But in the case of many hereditary diseases, the basic biochemical defect is unknown and, therefore, so is the nature of the gene. In such instances, mapping the disease gene requires family linkage studies using DNA or other markers. The Huntington's disease gene, assigned to chromosome 4 in 1983, was the first in an exciting succession of disease genes that have been mapped via family linkage methods.

Chromosomal banding methods have contributed as well, initially by providing a means for the unique identification of each chromosome. This was a boon to somatic-cell hybridization, as it permitted confident differentiation of the mouse and human chromosomes in the hybrid cells. More recently, high-resolution cytogenetics, ie, banding methods applied to the extended chromosomes of prophase or early prometaphase, have been used to detect small deletions and other abnormalities that serve as clues to the location of the genetic mutations responsible for several disorders, including various cancers. Such techniques have also figured in the localization of some wild-type genes.

The Mapping of Genes for Hormones and Growth Factors

Genes for hormones and growth factors have figured disproportionately in the mapping process, most likely because much information was already available concerning the molecular structure of these hormones and the enzymatic mechanisms by which they are synthesized. Figure 2 and Table 2 present the chromosomal loci of specific genes of endocrinologic interest. The genes for growth factor and growth factor receptors are listed in Table 3. Innate mutation of these genes may well turn out to be the cause of some hamartomatous conditions and other congenital disorders.

Although a discussion of proto-oncogenes, which now number 60 or more, is beyond the scope of this presentation, it is noteworthy that many of them are growth factors or growth factor receptors. An example of the former is *SIS* = platelet-derived growth factor, β subunit; of the latter, *FMS* = receptor for colony-stimulating factor-1 (CSF-1R). Furthermore, many oncogenes seem to function in a paracrine or autocrine manner to determine tumor histophenotype, as exemplified by neovascularization. All oncogenes serve a fun-

text continued on page 5

Figure 1 Growth in the field of gene mapping. The numbers relate exclusively to expressed genes.

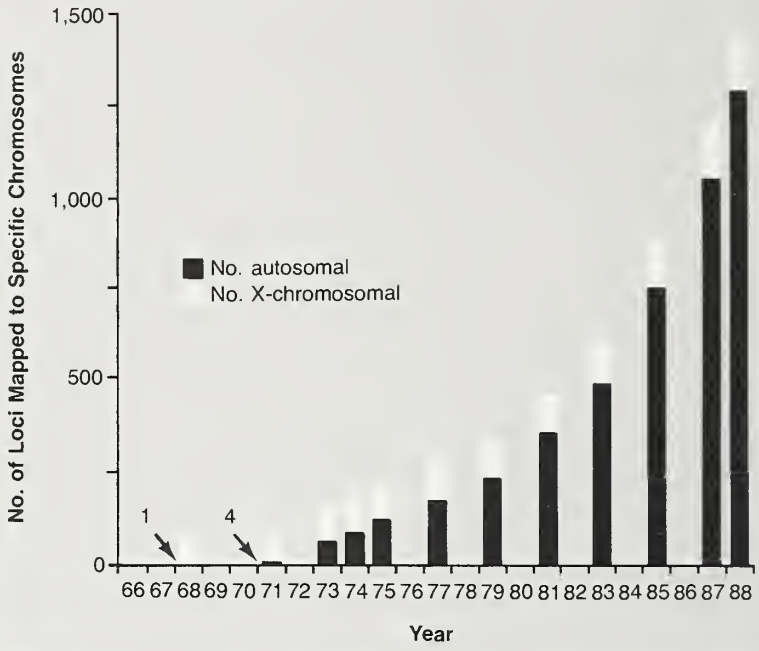


Table 1. Number of autosomal loci mapped by several methods (February 1, 1989)

Method	No. of Loci Mapped
Somatic-cell hybridization	889
In situ hybridization	444
Family linkage studies	382
Dosage effect	132
Chromosome aberrations	99
Restriction enzyme fine analysis	109
Homology of synteny	76
Radiation-induced gene segregation	18
Others	128
Total*	**2,277**

*The total exceeds the value of approximately 1,300 for autosomal gene loci mapped to date because many have been mapped by more than one method.

Figure 2 Maps of selected genes, particularly those of endocrinologic interest. The symbols are defined in Table 2.

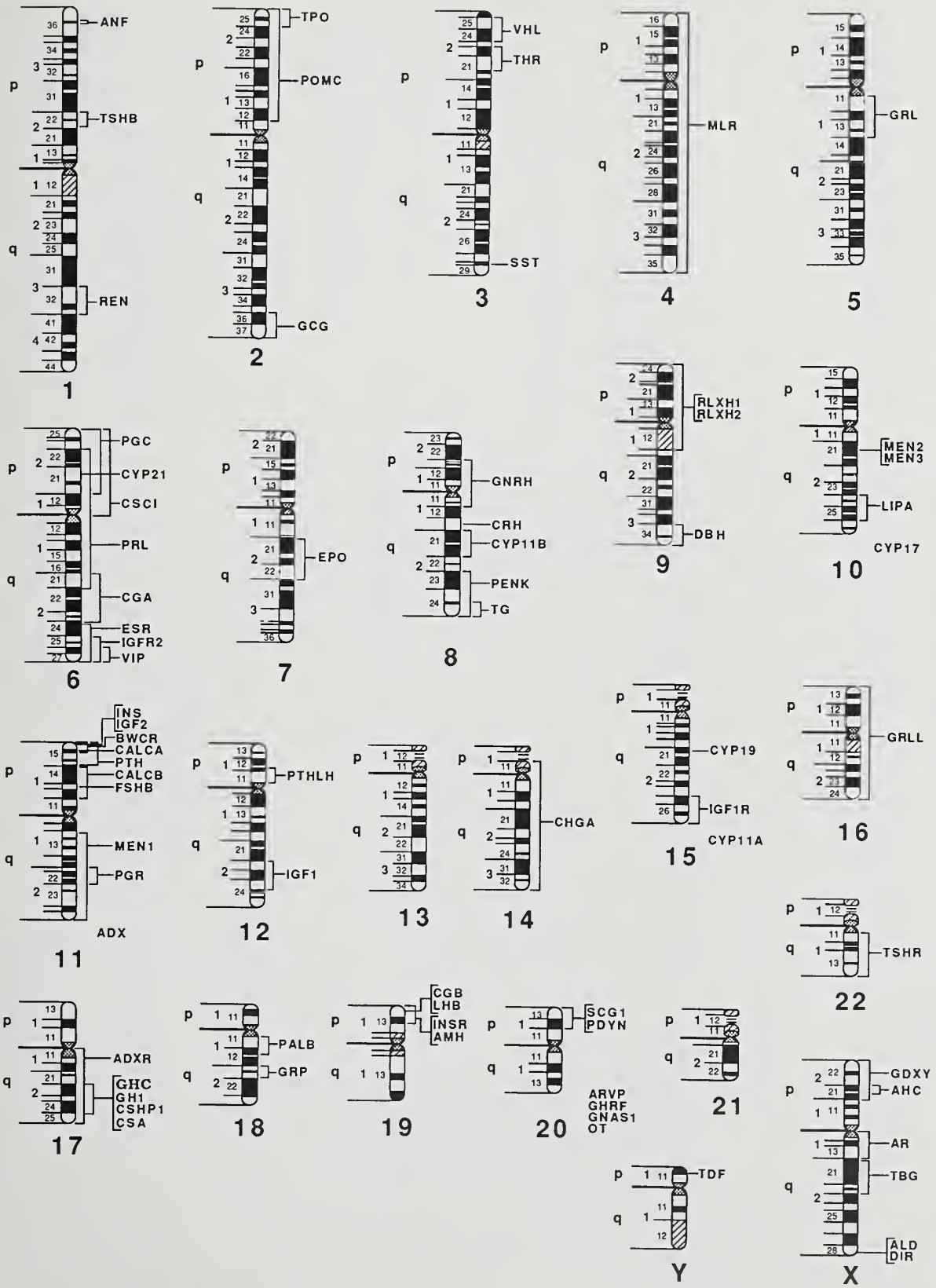


Figure 3 The "morbid map": location of mutations causing endocrinologic and growth disorders. (Boxes around the names of two or more disorders indicate that they are allelic, ie, caused by different mutations in one and the same gene.)

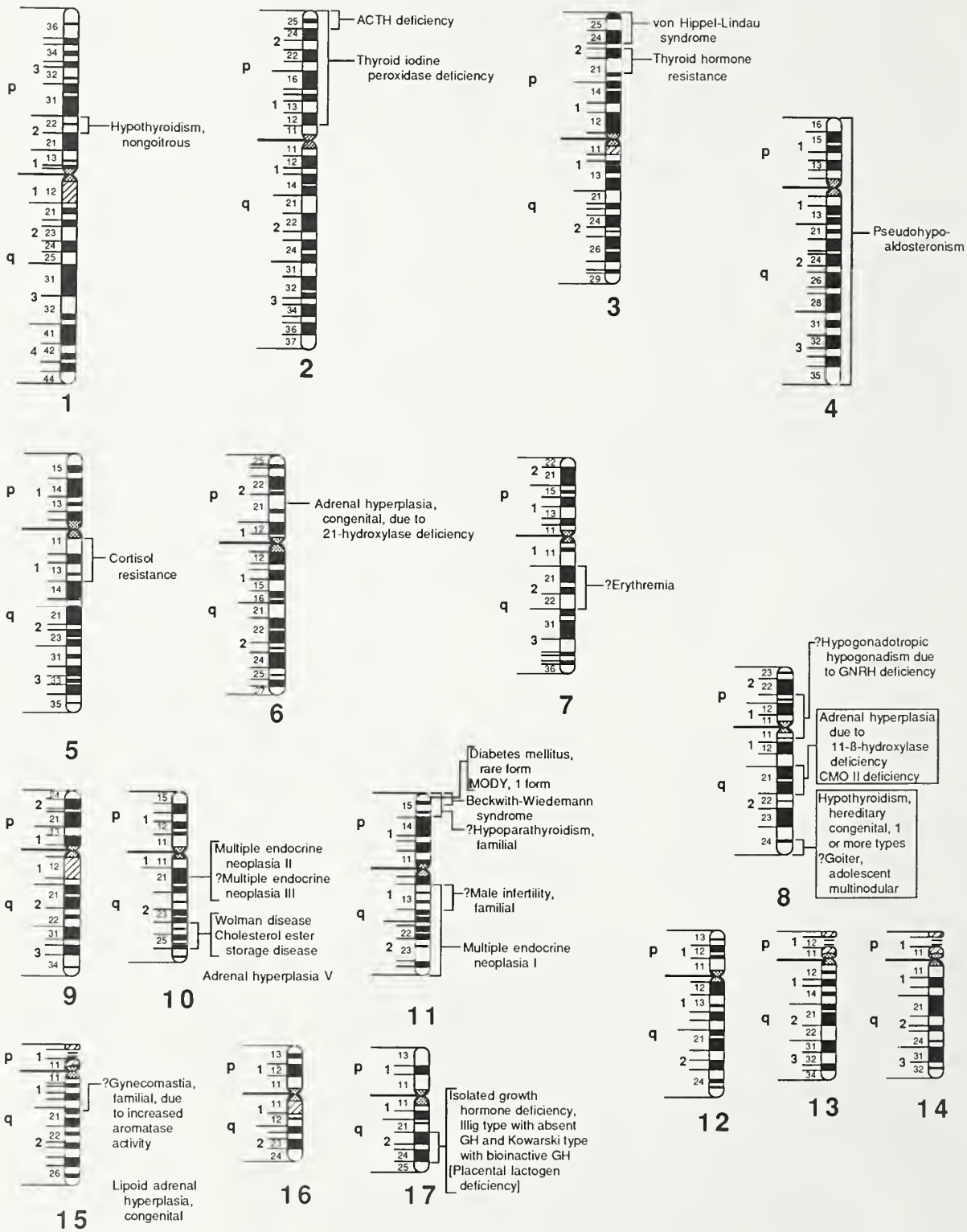
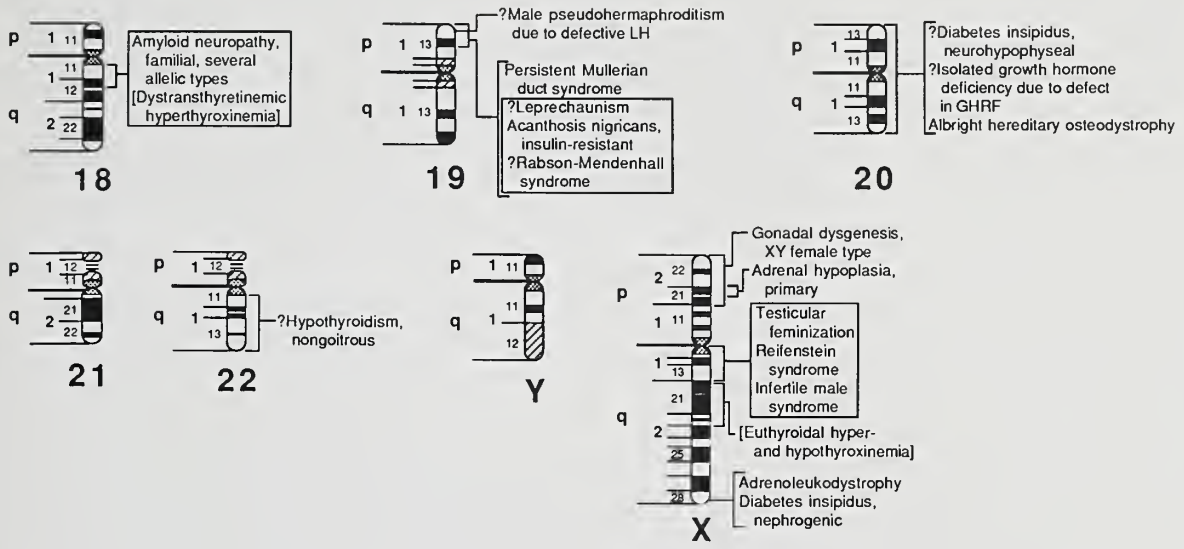


Figure 3 continued



damental role in normal cellular and tissue economy; the tumor-producing role is an aberration of the mutant form of the oncogene. In most instances, however, the normal functions are still unknown. The gene is not necessarily altered qualitatively when it produces cancer: amplification of a normal gene may also initiate a malignant process.

The Morbid Anatomy of the Human Genome

The arrangement of genes on our chromosomes is as much a part of our anatomy as our organ systems or our extremities. This anatomic metaphor (apart from the usual cartographic one) allows the human genome to be viewed in terms of its comparative anatomy and evolution, eg, its functional, developmental, applied, and morbid anatomy.[4] The chromosomal sites of the mutations responsible for many genetic disorders have now been determined by mapping either the wild-type gene or the disease phenotype or both. With this information, a morbid anatomy of the human genome has been constructed, and that which applies to the endocrinopathies and selected growth disorders is schematized in Figure 3.

Before concluding that a mutation is located at a particular site of a wild-type gene, one must be certain that the mutation involves that structural gene. Demonstration of a change in the DNA of the gene, such as deletion or nucleotide substitution, is incontrovertible evidence, provided that the nucleotide change is not a polymorphism. This was the type of evidence presented by Phillips and colleagues[5] for isolated growth hormone (GH) deficiency caused by the absence of the gene on chromosome 17.

Francomano and colleagues[6] used another method, known as the candidate-gene-linkage approach, to show that one form of Stickler syndrome is caused by mutation in the gene for cartilage (type II) collagen; no crossover was observed between the disease phenotype and RFLPs of the type II collagen gene. Another excellent example involves the entity responsible for generalized thyroid hormone resistance: tight linkage with the ERBA2 oncogene, which appears to be identical to the gene for thyroid hormone receptor (THR) on chromosome 3, was demonstrated by Usala et al in 1988.[7]

Examples of endocrinopathies in which the disease phenotype itself has been mapped include two forms of multiple endocrine neoplasia, MEN-1 and MEN-2, which are determined by mutations of the genes on chromosomes 11 and 10, respectively.

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Table 2. Gene loci of endocrinologic and related interest are listed here by the chromosome to which they have been mapped. Status: C = mapping confirmed; P = mapping provisional; L = mapping "in limbo" (tentative). MIM # = entry number in *Mendelian Inheritance in Man*[2] and its on-line version (OMIM). Method: A = in situ hybridization; C = chromosome-mediated gene transfer; Ch = chromosomal changes, visible; D = deletion mapping; EM = exclusion mapping; F = family linkage (Fc, with chromosomal heteromorphism or rearrangement; Fd, with DNA marker); H = homology mapping; HS = hybridization in solution; LD = linkage disequilibria; M = microcell-mediated gene transfer; OT = ovarian teratoma; R = Goss-Harris method of radiation-induced gene segregation and modification of Cox and Myers ("zap mapping"); RE = restriction endonuclease methods (REa, combined with somatic-cell hybridization; REb, combined with chromosome sorting; REn, neighbor analysis in large segments); S = somatic-cell hybridization; V = viral change. The numbers in parentheses in column 8 refer to the means by which the mutation was positioned: by mapping the wild-type gene (1), by mapping the disease phenotype (2), or by both approaches.

Location	*Symbol*	*Status*	*Title*	*MIM #*	*Method*	*Comments*	*Disorder*	*Mouse*
1p36.2	ANP, ANF, PND	C	Atrial natriuretic peptide; pronatriodilatin	10878	REa, A, H			4(Pnd)
1p22	TSHB	C	Thyroid stimulating hormone, beta subunit	18854	REa, RE, Fd	centromeric to NGFB	Hypothyroidism, nongoitrous (1)	3(Tshb)
1q32	REN	C	Renin	17982	REa, A, D	q32.3-q42.3 excluded by D; q42 = conflicting assignment		1(Ren-1)
2pter-p12	TPO, TPX	C	Thyroid peroxidase	27450	REa		Thyroid iodine peroxidase deficiency (1)	
2p25	POMC	C	Proopiomelanocortin	17683	REa	?close to ACP1	ACTH deficiency (1)	12(Pomc-1)
2q36-q37	GCG	C	Glucagon	13803	REa, A			2(Gcg)
3p25-p24	VHL	P	von Hippel-Lindau syndrome	19330	Fd	linked to RAF1	von Hippel-Lindau syndrome (1)	
3p22-p21.33	THR, THRB, THR1, ERBA2	C	Thyroid hormone receptor, beta (ERBA2)	19016	REa		?Thyroid hormone resistance, 27430, 18857 (1)	
3q28	SST	C	Somatostatin	18245	REa			16(Smst)
Chr.4	MLR, MCR, MR	P	Mineralocorticoid receptor	26435	REa, M		Pseudohypoaldosteronism (1)	
5q11-q13	GRL	C	Glucocorticoid receptor, lymphocyte	13804	S, REa		Cortisol resistance (1)	18(Grl-1)
6pter-p21.1	PGC	P	Preprogastricsin	16974	REa			
6p22.2-q21.3	PRL	C	Prolactin	17676	REa, D	?between 6ccn and GLO1		
6p21.3	CYP21, CA21H, CAH1	C	Congenital adrenal hyperplasia due to 21-hydroxylase deficiency; P450C21	20191	F, RE	linked to C2, C4, BF; 2 loci, A and B; only B active	Adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency (3)	17(P450-21)
6p	CSCI	L	Corticosterone side-chain isomerase	12255	H	?linked to MHC		
6q21.1-q23	CGA	P	Chorionic gonadotropin, alpha chain	11885	REa, A	shared with LH, FSH, TSH		4(Tsha)
6q24-q27	ESR, ER	C	Estrogen receptor	13343	REa, A			
6q25-q27	IGF2R, MPRI	P	Insulin-like growth factor-2 receptor (mannose-6-phosphate receptor, cation-indcpendent)	14728	REa, A			
6q26-q27	VIP	C	Vasoactive intestinal peptide	19232	REa, A, REb			
7q21-q22	EPO	C	Erythropoietin	13317	REa, A, REb	close to COL1A2; no recombination	?Erythremia (1)	5(Epo)
8p21-q11.2	GNRH, LHRH	P	Luteinizing hormone releasing hormone (gonadotropin releasing hormone)	15276	REa, A		?Hypogonadotropic hypogonadism due to GNRH deficiency , 22720 (1)	
8q13	CRH	P	Corticotropin releasing hormone	12256	REa, A			
8q21	CYP11B, P450C11	P	11-beta-hydroxylase; corticosteroid methyl oxidase II (CMO II)	20201	REa, A, Ch	multifunctional enzyme	Adrenal hyperplasia, congenital, due to 11-beta-hydroxylase deficiency (1); CMO II deficiency (1)	

Table 2. continued

Location	*Symbol*	*Status*	*Title*	*MIM #*	*Method*	*Comments*	*Disorder*	*Mouse*
8q23-q24	PENK	P	Proenkephalin	13133	REa, A			
8q24.2-q24.3	TG	C	Thyroglobulin	18845	A, REa, REb	distal to MYC	Hypothyroidism, hereditary congenital, 1 or more types (I); ?Goiter, adolescent multinodular, 13880 (1)	?15(Tg)
9pter-q12	RLXH1, RLN1	P	Relaxin, H1	17973	REa			
9pter-q12	RLXH2, RLN2	P	Relaxin, H2	17974	REa			
9q34	DBH	P	Dopamine-beta-hydroxylase	22336	F	tightly linked to ABO		
10q21.1	MEN2	C	Multiple endocrine neoplasia, type II	17140	Fd	19cM from D10S5 at 10q21.1	Multiple endocrine neoplasia II (2)	
10q21.1	MEN3, MEN2B	L	Multiple endocrine neoplasia, type III (or IIB)	16230	Fd	?allelic to MEN2	?Multiple endocrine neoplasia III(2)	
10q24-q25	LIPA	P	Lysosomal acid lipase-A	27800	S, H	?close to GOT	Wolman disease (I); Cholesterol ester storage disease (1)	19(Lip-1)
Chr.10	CYP17, P450C17	P	Steroid 17-alpha-hydroxylase / 17,20 lyase	20211	REa	at least 2 genes	Adrenal hyperplasia V (1)	
11pter-p15.4	BWCR, BWS, WBS	C	Beckwith-Wiedemann syndrome	13065	Ch	partial trisomy	Beckwith-Wiedemann syndrome (2)	
11p15.5	INS	C	Insulin	17673	HS, A, REb, Fd, D	5'--INS-12.6kb-IGF2--3'; cen-IIBBC-10cM-INS-2cM-IIRAS1-3cM-TH	Diabetes mellitus, rare form (1); MODY, 12585 (3)	6(Ins-1); 7(Ins-2)
11p15.5	IGF2	C	Insulin-like growth factor II, or somatomedin A	14747	REa, A, RE	separate gene for variant, 14741		
11p15.4	CALCA, CALC1	C	Calcitonin/calcitonin gene related peptide, alpha polypeptide	11413	REa, A, REb, D, Fd			7(Calc)
11p15	PTH	C	Parathyroid hormone	16845	REa, REb, A, Fd	ca.9cM distal to CALC1	?Hypoparathyroidism, familial (1)	7(Pth)
11p14.2-p12	CALCB, CALC2	C	Calcitonin gene related peptide beta	11416	A, REa, REb, D			
11p13	FSHB	C	Follicle stimulating hormone, beta polypeptide	13653	D, REa	distal to AN2	?Male infertility, familial (1)	2(Fshb)
11q13-qter	MEN1	C	Multiple endocrine neoplasia I	13110	Fd, D	linked to PYGM	Multiple endocrine neoplasia I (1)	
11q22	PGR	C	Progesterone receptor	26408	REa, A, REb	11q13 = earlier regionalization		
Chr.11	ADX	P	Adrenodoxin	10326	REa	pseudogene on 20		
12p12.1-p11.2	PTHLH	P	Parathyroid hormone-like hormone	16847	REa, A			
12q22-q24.1	IGF1	C	Insulin-like growth factor I, or somatomedin C	14744	REa, A			
Chr.14	CHGA	P	Chromogranin A (parathyroid secretory protein 1)	11891	REa			
15q21.1	CYP19, ARO	C	Cytochrome P450 aromatization of androgen (aromatase)	10791	REa, A		?Gynecomastia, familial, due to increased aromatase activity (1)	
15q25-q26	IGF1R	P	Insulin-like growth factor-1 receptor	14737	REa, A	?relation to FES		
Chr.15	CYP11A, P450SCC, P450C11A1	P	P450 side chain cleavage enzyme (20,22 desmolase)	20171	REa		Lipoid adrenal hyperplasia, congenital (1)	
Chr.16	GRLL	P	Glucocorticoid receptor, lymphocyte-like	13806	REb			
17cen-q25	ADXR	P	Adrenodoxin reductase	10327	REa			
17q22-q24	GHC	C	GROWTH HORMONE/PLACENTAL LACTOGEN GENE CLUSTER	13925	REa, A, C	17q22-q24		

Table 2. continued

Location	Symbol	Status	Title	MIM #	Method	Comments	Disorder	Mouse
17q22-q24	GH1, GHN	C	Growth hormone, normal	13925	REa, A	5'-GH1-CSHP1-CSH1-GH2-CSH2-3'	Isolated growth hormone deficiency, Illig type with absent GH and Kowarski type with bioinactive GH (3)	
17q22-q24	CSHP1, CSL	C	Chorionic somatomammotropin pseudogene	see 15020	REa, A			
17q22-q24	CSA, PL, CSH1	C	Chorionic somatomammotropin A	15020	REa, A		[Placental lactogen deficiency] (1)	
18q11.2-q12.1	PALB, TTR, TBPA	C	Thyroxine-binding prealbumin (transthyretin)	17630	REa, A		Amyloid neuropathy, familial, several allelic types (3); [Dystransthyretinemic hyperthyroxinemia](1)	
18q21	GRP	C	Gastrin releasing peptide	13726	REa, A	mammalian equivalent of bombesin		
19p13.3-p13.2	AMH, MIF	P	Anti-Mullerian hormone	26155	REa, A		Persistent Mullerian duct syndrome (1)	
19p13.3-p13.2	INSR	C	Insulin receptor	14767	REa, A, REb	1 gene for alpha and beta subunits	?Leprechaunism (1); ?Acanthosis nigricans, insulin-resistant (1); ?Rabson-Mendenhall syndrome (2)	8(Insr)
19q13.32	CGB	C	CHORIONIC GONADOTROPIN, BETA CHAIN	11886	REa, H, A	at least 5 genes		
19q13.32	LHB	C	Luteinizing hormone, beta chain	15278	RE	beta chains of FSH, TSH on 11p, 1p, respectively	?Male pseudohermaphroditism due to defective LH (1)	7(Lhb)
20pter-p12	SCG1, CHGB	P	Chromogranin B (secretogranin B)	11892	REa, A			
20pter-p12	PDYN	P	Prodynorphin	13134	REa, A			
Chr.20	AVP, VP	P	Arginine vasopressin-neurophysin II	19234	REa, RE		?Diabetes insipidus, neurohypophyseal, 12570 (1)	
Chr.20	GHRF	C	Growth hormone releasing factor; somatocrinin	13919	REa, REb		?Isolated growth hormone deficiency due to defect in GHRF (1)	
Chr.20	GNAS1, GNAS, GPSA	P	G-protein, stimulatory, alpha subunit (Gs-alpha)	13932	REa, H		Albright hereditary osteodystrophy (1)	2(Gs-a)
Chr.20	OT	P	Oxytocin-neurophysin 1	16705	RE	separated from VP by 12kb		
22q11-q13	TSHR	P	Thyroid stimulating hormone receptor	18846	REa		?Hypothyroidism, nongoitrous (1)	
Xp22-p21	GDXY, TDFX	P	Gonadal dysgenesis, XY female type	30610	F, Ch		Gonadal dysgenesis, XY female type (2)	
Xp21.3-p21.2	AHC, AHX	C	Primary adrenal hypoplasia	30020	D, Fd	distal to GK	Adrenal hypoplasia, primary (2)	
Xcen-q13	AR, DHTR, TFM	C	Testicular feminization (androgen receptor)	31370	S, Fd, REa, ?A		Testicular feminization (1); Reifenstein syndrome (1); Infertile male syndrome (1)	X(Tfm)
Xq21-q22	TBG	P	Thyroxine-binding globulin	31420	REa, A		[Euthyroidal hyper- and hypothyroxinemia] (1)	
Xq28	ALD	C	Adrenoleukodystrophy	30010	F, Fd, D	cone pigment gene deleted in some ALD males	Adrenoleukodystrophy (2)	
Xq28	DIR, DI1	C	Nephrogenic diabetes insipidus	30480	Fd		Diabetes insipidus, nephrogenic (2)	

Table 3. Genes for growth factors and growth factor receptors. (For definition of "status" and "MIM #," see Table 2.)

Location	*Symbol*	*Status*	*Title*	*MIM#*
1p22	NGFB	C	Nerve growth factor, beta	16203
2p13	TGFA	C	Transforming (or tumor) growth factor, alpha type	19017
4q25-q27	EGF	C	Epidermal growth factor	13153
4q26-q27	IL2, TCGF	C	T-cell growth factor (interleukin-2)	14768
5q23-q32	CSF2, GMCSF	C	Granulocyte-macrophage colony-stimulating factor	13896
5q31-q32	PDGFR	P	Platelet-derived growth factor receptor	17341
5q31.3-q33.2	ECGF	C	Endothelial cell growth factor	13122
5q33.1	CSF1, MCSF	P	Macrophage colony-stimulating factor	12042
5q33.2-q33.3	CSF1R, FMS	C	Oncogene FMS (McDonough feline sarcoma)	16477
6p23-q12	INSL	P	Insulin-like DNA sequence	14749
6q25-q27	IGF2R, MPRI	P	Insulin-like growth factor-2 receptor (mannose-6-phosphate receptor, cation-independent)	14728
7p13-p11	EGFR	C	Epidermal growth factor receptor	13155
7p21	IFNB2, IL6, BSF2	C	Interferon, beta-2 (hepatocyte-stimulating factor; interleukin-6)	14762
7p22-q21	PDGFA	C	Platelet-derived growth factor, A chain	17343
10p15-p14	IL2R, TAK	C	Interleukin-2 receptor; T-cell growth factor receptor	14773
12q22-q24.1	IGF1	C	Insulin-like growth factor 1, or somatomedin C	14744
15q25-q26	IGF1R	P	Insulin-like growth factor 1 receptor	14737
17q21	CSF3, GCSF	C	Granulocyte colony-stimulating factor-3	13897
17q21-q22	NGFR	C	Nerve growth factor receptor	16201
19q13.1-q13.3	TGFB	P	Transforming (or tumor) growth factor, beta form	19018
22q12.3-q13.1	SIS,PDGFB	C	Oncogene SIS (platelet-derived growth factor, B chain)	19004
Chr.4	FGFB	P	Fibroblast growth factor, basic	13492
Chr.5	FGFA	P	Fibroblast growth factor, acidic	13491
Chr.7	IBP1	P	Insulin-like growth factor, low molecular weight	14673
Chr.?	BCGF		B-cell growth factor	10954
Chr.?	CSF2R		Granulocyte-macrophage colony-stimulating factor receptor	13898
Chr.?	FGF5		Oncogene fibroblast growth factor-5	16519
Chr.?	NGFA		Nerve growth factor, alpha polypeptide	16202
Chr.?	NGFG		Nerve growth factor, gamma polypeptide	16204

Pheochromocytoma occurs in neurofibromatosis, which maps to proximal 17q, and in von Hippel–Lindau syndrome, which maps to 3p. These disorders all were mapped by linkage to RFLP markers.

Primary adrenal hypoplasia is encoded by a mutation located on Xp21 and another adrenal disorder, adrenoleukodystrophy, by a mutation on the Xq28 band. Nephrogenic diabetes also is determined by a mutation on the Xq28 band. Other interesting entities in this category include X-linked hypoparathyroidism, encoded at Xq26-q27; DiGeorge syndrome with hypoparathyroidism, at the proximal part of 22q; and the Beckwith-Wiedemann syndrome, in which cellular overgrowth includes nesidioblastosis of the pancreas with hypoglycemia, at the tip of chromosome 11p.

The Applied Anatomy of the Human Genome

Mapping information has been particularly useful in the case of disorders for which the basic biochemical defect is not known. Great interest has been generated by the announcements of chromosomal mapping of the genes for Huntington's disease, cystic fibrosis, adenomatous polyposis of the colon, polycystic kidney disease, von Recklinghausen neurofibromatosis, Alzheimer's disease, Duchenne muscular dystrophy, and many others. Prior to mapping, no diagnostic means or rational therapy could be devised for any of these conditions. Once a marker closely situated to the locus of a mutant gene is known, however, genetic diagnosis can be done by the linkage principle, which involves prenatal and preclinical sampling and carrier detection within a given family.

Furthermore, with neighboring or, better still, flanking markers, one can hope to walk in on the segment of DNA that contains the mutant gene and thereby identify both the gene and the precise nature of the change. This is so-called reverse genetics. Knowing the nature of the mutated gene opens the possibility of reconstructing the pathogenetic steps between gene and phene and devising therapeutic measures (short of gene replacement or repair) for ameliorating the effects of the disorder.

Defining the intragenic lesion is to chromosome mapping what microscopic anatomy is to gross anatomy. With every Mendelian disorder there must be a lesion in the DNA, and, increasingly, we will have the capability of going directly to the DNA—obtained from

circulating leukocytes, for example — to determine whether the lesion characteristic of a specific disorder is present. Indeed, this procedure might be called a biopsy of the human genome. John Phillips and colleagues[5] provided an early illustration of this approach when they demonstrated deletion of the GH gene on chromosome 17 in cases of isolated GH deficiency of the Illig type (type 1A). In other cases of isolated GH deficiency, they could exclude mutation in the structural gene by the linkage principle: affected sibs had inherited different chromosomes (17) from the parents, as indicated by RFLP markers, and no rearrangement or other structural abnormality of the GH gene could be identified by Southern blot analysis.

Conclusions

Gene mapping is a technique that has expanded diagnostic and therapeutic potential immensely in the past decade. If adequate resources are made available, the human genome will be rapidly identified in its entirety. The implications are of great pertinence not only to geneticists but also to endocrinologists, nutritionists, and pediatricians. The reader is encouraged to follow closely this rapidly developing field, from which future genetics and endocrinology will evolve.

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To the Editor:

The article by A.D. Rogol, "Anabolic Steroid Hormones for Athletes: Efficacy or Fantasy?" (*Growth, Genetics, and Hormones*, December 1988; Vol. 4, No. 4), emphasizes the toxicity of these substances while failing to credit the known facts about their pronounced anabolic properties. It was a half century ago that Charles Kochakian and John R. Murlin first demonstrated the nitrogen-retaining properties of anabolic steroids[1]; later work showed increased muscle mass in experimental animals. Dr. Rogol correctly states that testosterone is principally responsible for the sex difference in muscle mass and strength that evolves during puberty.

What is generally not appreciated is the dose-dependent effect of anabolic steroids.[2,3] The small doses (total < 500 mg) used by some investigators produce very small amounts of nitrogen retention and increments in lean weight, so one would not expect significant increases in muscle strength. At total doses greater than 2,000 mg, there is a progressive increase in lean weight, as estimated by potassium 40 counting and total body nitrogen, and a fall in body fat. Under these circumstances the effect on lean body mass is far greater than has been reported from physical exercise and/or training alone. Moreover, Alén et al[4] have shown that large doses of anabolic steroids do indeed augment muscle strength and individual muscle fiber area, and to a much larger degree than does training alone. This is why athletes take steroids.[5]

Dr. Rogol supplies no evidence in support of his claims that anabolic steroids cause edema and that weight is quickly lost when they are discontinued. In our experience (R.C. Griggs, unpublished data) with several adult volunteers given anabolic steroids, it took 1 month or more for body weight and lean body mass to return to baseline after discontinuation of the drug.

Whatever our feelings about the use of anabolic steroids by athletes, we must admit that steroids truly are *anabolic*. We cannot dissuade people from taking them by downplaying the effects that are only too evident to the athletes themselves.

Gilbert B. Forbes, M.D.
University of Rochester Medical Center
School of Medicine and Dentistry
Rochester, New York

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In Future Issues

Inflammatory Bowel Disease and Growth Retardation
by Richard Grand, M.D.

Growth Hormone and IGF-1: Independent and Dependent Actions
by Olle Isaakson, M.D.

Growth in Late Adolescence
by Alex Roche, M.D.

Testicular Differentiating Factor: The Gene and its Clinical Importance
by Barbara Mc Gillivray, M.D.

Mechanisms Responsible for Normal Bone Growth
by William Horton, M.D.

Paracrine Aspects of Bone Metabolism
by David Baylink, M.D.

Dr. Rogol's Reply

I thank Dr. Forbes for his letter regarding my article in *Growth, Genetics, and Hormones*. Dr. Forbes correctly points to the strong dose dependency (above a threshold level) of increase in lean body mass in most controlled studies. He refers to the work of Alén and co-workers, who have shown that "large" doses of androgenic steroid hormones augment muscle size as determined by morphometric analysis. However, there are many other studies that are equivocal or poorly executed. Although I agree that large doses of androgenic steroid hormones most likely augment lean body mass, there is great controversy over the magnitude of the effect and its precise mechanism.

My comment concerning the possibility that edema is partially responsible for weight gain following the use of androgenic steroid hormones is indeed anecdotal, but marked weight loss within 24 hours of a weight-lifting competition (enabling the lifter to compete in a lower body-weight class) probably can be ascribed mainly to fluid loss. Dr. Forbes, in his own work[1] concerning the effect of testosterone on muscle mass, states this possibility: "The increase in body weight [following testosterone enanthate, 3 mg/kg intramuscularly each week for 12 weeks] could reflect a gain in water, but the increase in creatinine excretion, serum creatinine, and total body potassium *suggests* an increase in muscle mass [italics added]."

The controversy over the anabolic effects of androgenic steroid hormones persists. It is likely, in my opinion, that large doses are in fact anabolic and increase muscle strength and athletic performance in *some* sports. It has not, however, been proved beyond a reasonable doubt that this is so. Athletes, being supreme pragmatists, will use steroids if they perceive that these compounds are helpful, even if they do not know the mechanism of action—which may be anticatabolic just as easily as anabolic.

Alan D. Rogol, M.D., Ph.D.
University of Virginia
School of Medicine
Charlottesville, Virginia

Reference

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To the Editor:

I was delighted to read the much-needed review article entitled "Lipodystrophy" by William L. Clarke (*Growth, Genetics, and Hormones*, September 1988; Vol. 4, No. 3). I would like to add our experience with an additional, albeit rare, form of lipodystrophy to those reviewed by Dr. Clarke. An autosomal dominantly inherited form of partial lipoatrophy that spares the head and neck was first described by Dunnigan[1] and again by Kobberling.[2] In the literature, this entity hence has been referred to as Kobberling-Dunnigan syndrome or, alternatively, face-sparing lipoatrophy. To date, six families with the syndrome have been reported in the literature. We have encountered this syndrome in two additional kindreds, one of which encompasses three generations and includes 30 affected individuals. Like those with the other forms of lipodystrophy that were reviewed, the patients we have observed have insulin-resistant diabetes, acanthosis nigricans, elevated triglyceride levels, and hepatomegaly. Although Kobberling-Dunnigan syndrome is rare, it may be distinguished from the sporadic, acquired type of lipodystrophy by its dominant inheritance. Whenever a face-sparing distribution of lipoatrophy is observed, a detailed family history should be obtained to rule out this genetic form.

Catherine McKeon, Ph.D.
Senior Staff Fellow
National Institute of Diabetes and Digestive and Kidney Diseases
Bethesda, Maryland

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2. Kobberling J. *Humangenetik* 1975; 29:111-120.

Dr. Clarke's Reply

We thank Dr. McKeon for her important letter. We would agree that the Kobberling-Dunnigan syndrome probably is another form of inherited lipodystrophy. The paucity of case reports and information on this rare disorder led us to exclude it from our review. It is important that physicians accurately report their experiences with the lipodystrophic syndromes in the literature, so that a better understanding of these syndromes may be attained.

Address for Correspondence

Please send all correspondence to

Robert M. Blizzard, M.D.
Department of Pediatrics
University of Virginia
School of Medicine
Charlottesville, VA 22908.

Acromegaly in an Infant

In discussing this case of a 21-month-old girl with excessive levels of growth hormone (GH; 135 ng/mL), prolactin (Prl; 370 ng/mL), and insulin-like growth factor–1 (IGF-1; 1,540 ng/mL), whose height was 97.6 cm (+4.4 SD) and whose head circumference was 55 cm (+5.5 SD), the authors briefly reviewed 22 cases of acromegaly reported in childhood. The majority had rapid linear growth, coarse facial features, and enlarged hands and feet; these are symptoms comparable to the findings that are discussed in the article. Interestingly, the 21-month-old girl had rapid head growth that preceded the significant rapid body growth. The authors postulate that the macrocephaly occurred because of rapid brain growth.

After a macroadenoma was removed from the suprasellar area, the GH and IGF-1 levels fell into the low normal range for preadolescent children. With pharmacologic testing, GH concentrations did not increase beyond 4 ng/mL, and Prl levels remained significantly elevated. GH-producing cells, but no Prl-producing cells, were observed under the microscope, utilizing immunologic techniques. The integrated GH concentration remained relatively stable overnight (~ 2 ng/mL), and peak GH concentrations did not exceed 3 ng/mL. The authors profess perplexity because this patient continued to grow at 6 cm/y over the next 2 years. Three possible explanations are offered: (1) hyperinsulinemia, which they subsequently exclude on the basis of insulin levels found during performance of a glucose tolerance test; (2) the continuing secretion of low levels of GH overnight, also discounted because the integrated GH value reportedly is lower than values obtained in control subjects; and (3) the elevated Prl levels, which contributed to the normal IGF-1 levels and the sustained growth. Several references are cited to support the final hypothesis.

In reviewing the literature, the authors note that hyperprolactinemia occurred in 12 of 15 pediatric cases. In seven cases where the tumor was examined by immunohistochemical techniques, both Prl and GH were present. In contrast, only GH was found in the case under discussion. The authors postulate, therefore, that disruption of the inhibitory centers and/or tracts accounted for the hyperprolactinemia in this patient.

Blumberg DL, Sklar CA, David R, et al. *Pediatrics* 1989;83: 998-1002.

Editor's comment—*This article provides stimulating reading for pediatric endocrinologists. It updates the count of children reported with acromegaly and the immune histochemical findings in the pituitary of these children. It also raises again the question regarding the capability of Prl to increase IGF-1 levels. The postoperative Prl levels in this girl were 30 to 120 ng/mL. Previously, Clemmons et al (*J Clin Endocrinol Metab *1981;52:731) reported Prl levels greater than 100 ng/mL associated with normal adult IGF-1 levels in 20 GH-deficient patients. Very possibly, we as clinicians do not pay adequate attention to the role that increased Prl levels may play in producing normal IGF-1 levels in GH-deficient patients. All "suspect" GH-deficient patients whose IGF-1 is not in the GH-deficient range should be screened for high Prl.*

Robert M. Blizzard, M.D.

Verification of the Fetal Valproate Syndrome Phenotype

Valproic acid (VPA) is a relatively new anticonvulsant that was approved for use in the United States in 1978. Its main indication is for the treatment of absence seizures, although it has been used, often in combination with other anticonvulsants, to treat a variety of other seizure disorders.

In 1984, DiLiberti et al described a consistent facial phenotype in seven children who were exposed to VPA in utero. The facial abnormalities included epicanthic folds, flat nasal bridge, small upturned nose, long upper lip, shallow philtrum, thin lower lip, and downturned mouth. The authors also suggested an association of this phenotype with other anomalies, such as low birth weight, psychomotor delay, congenital heart defects, neural tube defects, hypospadias, strabismus, and nystagmus.

In the current study, 19 children who were exposed to VPA in utero were carefully examined. No consistent alterations of pre- or postnatal growth deficiency were found with exposure to VPA alone. Postnatal growth deficiency and microcephaly were present, however, in two thirds of the children exposed to VPA in combination with other anticonvulsants. Developmental delay or neurologic abnormality was found in 71% of those exposed to VPA alone and in 90% of those exposed to VPA and other anticonvulsants. Craniofacial anomalies, which can be seen in children exposed to other anticonvulsants in utero, were also found in infants whose mothers received VPA. The anomalies included midface hypoplasia; short nose with a broad and/or flat bridge; epicanthic folds; minor abnormalities of the ear, philtrum, or lip; and micrognathia. Prominent metopic ridge and outer orbital ridge deficiency or bifrontal narrowing, and certain major anomalies such as tracheomalacia, talipes equinovarus, and lumbosacral meningomyelocele, seem to be peculiar to infants with VPA exposure.

Ardinger HH, Atkin JF, Blackston RD, et al. *Am J Med Genet* 1988; 29:171.

Editor's comment—*The authors confirm the presence of a distinct fetal valproate syndrome that shares many features with the other syndromes secondary to prenatal exposure to anticonvulsants, ie, developmental delay, craniofacial abnormalities, congenital heart defects, urogenital anomalies, and limb anomalies. In contrast to the fetal diphenylhydantoin, trimethadione, and phenobarbital/primidone syndromes, neither prenatal nor postnatal growth deficiency is present in the fetal VPA syndrome. Indeed, only those children who were exposed to VPA and another anticonvulsant in utero had growth deficiency. Thus, each of the commonly used anticonvulsants appears to produce a distinct fetal malformation syndrome phenotype. It is most important, as the authors have done in this study, to isolate the specific effects of each of the anticonvulsants since so many women requiring treatment for seizures take more than one.*

David L. Rimoin, M.D., Ph.D.

Development of Human Palmar and Digital Flexion Creases

Normal flexion creases of the fingers and palm reflect normal movement and development of the upper limbs during embryonic and fetal life. A study by Stevens and colleagues of the flexion creases in the human fetus has established the time during fetal life when these creases first appear. A hand malformation or specific insult that occurs before the time of crease development may cause secondary alterations in crease patterns of the hand. The presence of creases may also be used to date the age of an abortus.

The authors measured the development of hand creases by examining the hands of 100 human fetuses that had been obtained by random selection after therapeutic abortion. At 7 weeks' gestation, the fingers are separated but the hand is smooth and glove like, without pads, creases, or distinguishing features between the dorsal and volar surfaces. At 8 weeks, the distal interphalangeal and metacarpophalangeal creases are faintly visible. Digital and interdigital pads begin to be seen, and the thumb begins to rotate to another plane. At 9 weeks, the proximal interphalangeal and thenar creases become visible, and the nail beds begin to form. At 10 weeks the digital creases are well formed. The interdigital pads begin to regress, and a depression is seen in the center of the digital pads. Thickenings appear in the palm, and the nails are well defined. At 11 weeks, the distal palmar creases appear. At 12 weeks, the proximal palmar creases are seen and the digital pads are still present, but the interdigital pads are gone. By 13 weeks, all palmar and digital creases are well defined, digital pads are regressing, and the thumb is opposable. The digital pads disappear by 15 weeks.

This work establishes the normal pattern and development of digital and palmar creases.

Stevens CA, Carey JC, Shah M, et al. *J Pediatr* 1988;113:128-132.

Editor's comment—*Creases of the hand are examined in all children. With specific dating of the development of these creases, we can much more accurately time insults and abnormalities. This study makes a real contribution to defining normal development.*

Judith G. Hall, M.D.

Transient Growth Deceleration in Normal Short Children: A Potential Source of Bias in Growth Studies

A child whose growth fluctuates from one 6-month period to the next is more likely to be diagnosed as growth hormone (GH) deficient at the end of the slow growth period than at the end of the rapid growth period. Under these circumstances there is a strong selection bias, and one would expect a regression toward the mean velocity during the 6 months after diagnosis, whether or not the child was treated. To test this hypothesis, the authors followed 21 short children who had 6-month growth velocities < 4 cm/y but whose response to GH stimulation testing was >5 ng/mL and showed that they were not GH deficient. All but three of the children had increases in velocity > 0.5 cm/y during the subsequent 6 months of observation. These increases were significant in both the prepubertal and pubertal groups: the mean growth rates increased from 3.4 to 5.1 cm/y and from 3.4 to 6.3 cm/y, respectively. In growth studies in which children are used as their own controls, this effect must be taken into account.

Polychronakos C, Abu-Srair H, Guyda HJ. *Eur J Pediatr* 1988; 147:582.

Editor's comment—*"Regression toward the mean" is an important aspect of any longitudinal study in which the initial value is not based on a random selection from the population. It stems from unreliability of measurement, as well as from seasonal and other fluctuations. In any growth study in which a treatment is given after a control period, the most likely velocity in the absence of treatment must be estimated. Bias is introduced, however, if the most likely velocity is estimated simply as a continuation of the velocity in the control period.*

James M. Tanner, M.D., D.Sc.

Atlantoaxial Instability in Down Syndrome

At least 10% of individuals with Down syndrome have atlantoaxial instability, as measured by an atlantodens interval of >5.0 mm. Because of the risk of spinal cord damage, Special Olympics, Inc., and the American Academy of Pediatrics have recommended evaluation, including cervical roentgenography, for all individuals with Down syndrome who wish to take part in sports.

Davidson recently reviewed the evidence that individuals with Down syndrome are at increased risk for unexpected spinal cord injury when taking part in sports. He found that in almost all published cases of spinal cord injury in Down syndrome patients there had been signs or symptoms of cervical subluxation for weeks or months prior to the injury. He points out in his review that the incidence and real risk of cervical subluxation, the results of longitudinal studies in cases of Down syndrome with atlantodens intervals > 5.0 mm, and the exact measurements that should lead to concern at a particular age have not been defined. Thus, exclusion from sports may be inappropriate unless the individual has had a roentgenographic series or studies of cervical spine flexion and extension. He does agree that sports that lead to

New Concepts of the Growth Spurt of Puberty

The authors emphasize that *final height attained is independent of the timing and intensity of the growth spurt.* Thus, those who enter puberty late have a relatively smaller growth velocity (GV) during the adolescent growth spurt, and they reach a final height identical to what it would have been had they entered puberty earlier and experienced a greater GV for a shorter period. A previous article by these investigators reported that short normal children and children with central precocious puberty (CPP) who had puberty arrested with a gonadotropin-releasing hormone agonist-analog (GnRHa) did not have an improved height prognosis.

The authors attribute the earlier onset of puberty in girls, compared with boys, to differences in luteinizing hormone (LH) pulsatility. Girls require lower doses of luteinizing hormone–releasing hormone (LHRH) to cause the release of LH than do boys, and LHRH agonist-analogs (LHRHa) block the release of LH more readily in girls than in boys. These observations may also help to explain why CPP is more common in girls than in boys and why the converse is true of constitutional growth delay.

The timing of the growth spurt is related to an increase in growth hormone (GH) production, particularly to the amplitude of the GH peaks, according to the authors. GV and GH secretion peaked when the testicular volume reached 12 mL in boys; in girls, this correlation was noted before any increase in serum estradiol or uterine size was detected by ultrasonography. The evidence suggests that changes in GH secretion are modulated by factors other than sex steroids, and the recent demonstration that inhibin can affect the GH response to growth hormone–releasing hormone (GHRH) (*J Endocrinol* 1988;116:301) may be relevant.

In discussing the effect of GnRH on growth in CPP, the authors state that GnRHa do *not* increase ultimate height. This phenomenon relates to the decreased GH production that occurs with the use of GnRHa. The researchers postulate that GH given concomitantly with GnRHa may play a beneficial role and that delay in the timing of puberty alone will probably not improve final height prognosis.

Stanhope R, Preece MA, Grant BD, et al. *Acta Paediatr Scand* 1988;347(suppl):30.

Editor's comment—*The studies reported and the concepts proposed are well worth reading in detail. The growth spurt of adolescence undoubtedly is attributable to increased GH production, as reported by Martha et al at the Society for Pediatric Research meetings in May 1989. Boys in stages 3 and 4 of sexual development have GH levels two to three times those found during stages 1 and 2 of puberty and after epiphyseal fusion occurs. There is a strong correlation among GV, GH production, and insulin-like growth factor–1 generation, as demonstrated in those studies. As for the lack of effectiveness of GnRHa in enhancing the ultimate height of girls with CPP, I disagree. Table 2 in the Boepple and Crowley article (*Growth, Genetics, and Hormones *March 1989; Vol. 5, No. 1) clearly indicates that the appropriate use of GnRHa prevents the loss of height that occurs in patients with untreated CPP. Among such children, those with a bone age greater than 13 years have an average predicted adult height of −3.7 SD. Patients with treated CPP whose bone ages at the time of treatment are less than 10 years remain at essentially the same mean score (−1.1 for bone age) after 3 years of GnRHa treatment.*

Robert M. Blizzard, M.D.

hyperextension or radical flexion of, or direct pressure on, the neck or spine (eg, tumbling or trampolining) may place the patient in jeopardy. It is possible that car accidents, rheumatoid disease, and general anesthesia also may increase the risk of spinal cord injury in individuals with Down syndrome. Interestingly, the number of injuries leading to symptoms of subluxation appears to be increasing in girls and women with Down syndrome.

Davidson RG. *Pediatrics* 1988; 81:857-865.

Pueschel SM. *Pediatrics* 1988; 81:879-880.

Atlantoaxial instability in Down syndrome. Editorial. *Lancet* 1989; 1:24.

Editor's comment—*What should we recommend to the families of individuals with Down syndrome concerning sports participation? Clearly, better information is needed to define the risks and make appropriate recommendations for studies and follow-up. The crucial issue is, Are we going to do unnecessary testing and unnecessarily restrict activities in the name of safety?*

Judith G. Hall, M.D.

Identification of the Molecular Defect in a Family With Spondyloepiphyseal Dysplasia

The problem of gene defects is of intense interest to geneticists and molecular biologists. The spondyloepiphyseal dysplasias (SED) are a heterogeneous group of inherited disorders characterized by disproportionately short stature and pleiotropic involvement of the skeletal and ocular systems. Recent investigations suggest an association between some forms of SED and a defect in type II collagen. In this study coarse scanning by Southern blot hybridization of the *COL2A1* gene, which encodes type II collagen, identified an abnormal restriction pattern in the DNA of one of the affected members of a relatively large family with SED. Analysis of selected genomic fragments localized the molecular defect, all affected family members carried the same heterozygous single-exon deletion.

The proband was a 3.5-year-old girl, apparently normal at birth, who had a history of ear infections, slowed growth, and genu valgum. She was short and had lordosis, mild kyphosis, and rhizomelic shortening of the extremities. Epiphyseal centers were affected with no metaphyseal involvement. The father, four paternal aunts, and two nieces had kyphoscoliosis, retinal detachment, myopia, genu valgum, cervical instability, and dwarfism. Analysis of the proband's DNA yielded a novel 3.3-kb *Eco*RI fragment that was not seen in the control samples. This segment of *COL2A1* contains exons 45 to 52, which code for the C-terminal propeptide and the last 123 amino acid residues of the triple-helical domain. Amplification of *COL2A1* exons 47 to 52 from genomic DNA of unaffected family members produced a single 3.2-kb fragment. Analogous amplifications of DNA from affected family members produced the normal 3.2-kb fragment and a deleted 2.8-kb fragment. This finding established the segregation of the deleted *COL2A1* allele with the abnormal SED phenotype. The deletion accounts for the elimination of the whole of exon 48, including 36 amino acids of the type II triple-helical domain. The authors conclude that the *COL2A1* deletion is responsible for this type of dwarfism.

Lee B, Vissing H, Ramirez F, et al. *Science* 1989;244:978.

Editor's comment—*Chondrodysplasias are a highly heterogeneous group of disorders that includes endochondral ossification and simple abnormal skeletal growth. These entities are believed to result from mutations affecting either the structural integrity of cartilage matrix components or the regulatory pathways of chondrogenesis.* COL2A1 *has been linked to the Stickler syndrome by genetic analysis, and, as noted by the authors, biochemical analysis of small cartilage samples from chondrodysplastic individuals has recently suggested that some of these conditions, such as the spondyloepiphyseal dysplasias, Kniest dysplasia, and type II achondrogenesis-hypochondrogenesis, may be associated with type II collagen defects. The association seems to be confirmed for this particular family with SED.*

Fibroblasts from patients with osteogenesis imperfecta have a type I collagen defect, and defects in type III collagen have been demonstrated in patients with Ehlers-Danlos syndrome. In these disorders, structural mutations in the type I and type III collagen subunits are believed to decrease the rate of helical assembly and expose greater regions of unassembled chains to overmodification. The location of a defect within the helical domain may affect directly the degree of collagen modification.

Robert M. Blizzard, M.D.

November 12-15 The 40th Annual Meeting of The American Society of Human Genetics, Convention Center, Baltimore, Maryland. Contact: Jean Francese, American Society of Human Genetics, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1825)

January 10-13, 1990 37th Postgraduate Course, American Diabetes Association. Hyatt Regency Grand Cypress, Orlando, Florida. Contact: American Diabetes Association, 1660 Duke Street, Alexandria, VA 22314 (800-232-3472)

February 4-8, 1990 17th Annual Seminar in Pediatric Nephrology: Current Concepts in Diagnosis and Management. Diplomat Resort and Country Club, Hollywood, Florida. Contact: Pearl Seidler, Division Coordinator, Department of Pediatrics, Division of Pediatric Nephrology, University of Miami School of Medicine, P.O. Box 016960, Miami, FL 33101 (305-549-6726)

February 6-9, 1990 Joint Meeting of the Western Section of the American Federation of Research and the Western Society for Pediatric Research. Various locations in Carmel, California. Contact: David K. Stevenson, M.D., Department of Pediatrics, Room S222, Stanford University School of Medicine, Stanford, CA 94305 (415-723-5711)

April 28-May 3, 1990 Spring Session, American Academy of Pediatrics. Seattle, Washington. Contact: Department of Education, American Academy of Pediatrics, P.O. Box 927, Elk Grove Village, IL 60007 (800-322-9016)

May 7-11, 1990 Annual Meeting of the American Pediatric Society/ Society for Pediatric Research/ Ambulatory Pediatric Association. Hilton Hotel, Anaheim, California. Contact: Debbie Anagnostelis, Executive Director, Society for Pediatric Research, 2650 Yale Boulevard S.E., Suite 104, Albuquerque, NM 87106 (505-764-9099)

May 9, 1990 Diabetes Symposium, Lawson Wilkins Pediatric Endocrine Society. Hilton Hotel, Anaheim, California. Contact: Gilbert August, M.D., Department of Endocrinology and Metabolism, Children's Hospital, 111 Michigan Avenue N.W., Washington, DC 20010 (202-745-2121)

May 11, 1990 Annual Scientific Session, Lawson Wilkins Pediatric Endocrine Society. Hilton Hotel, Anaheim, California. Contact: Gilbert August, M.D., Department of Endocrinology and Metabolism, Children's Hospital, 111 Michigan Avenue N.W., Washington, DC 20010 (202-745-2121)

June 8-11, 1990 30th Meeting of the Teratology Society. Empress Hotel and Convention Center, Vancouver, British Columbia, Canada. Contact: Alexandria Ventura, Administrative Assistant, Teratology Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1841)

June 20-23, 1990 72nd Annual Meeting of The Endocrine Society. Atlanta Convention Center, Atlanta, Georgia. Contact: Scott Hunt, Executive Director, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

July 9-11, 1990 Annual March of Dimes Clinical Genetics Conference: Gastrointestinal Disorders. Westin Hotel, Detroit, Michigan. Contact: Orlando J. Miller, M.D., Wayne State University, 2316 Scott Hall, 540 East Canfield Avenue, Detroit, MI 48201 (313-577-5323)

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Robert M. Blizzard, M.D.
c/o Healthcare Education Division
McGraw-Hill Healthcare Group
800 Second Avenue
New York, NY 10164-0569

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Testicular Differentiating Factor: Current Concepts

Barbara C. McGillivray, M.D.
Associate Professor
University of British Columbia
Co-director, Prenatal Diagnosis Program
Grace Hospital
Vancouver, British Columbia
Canada

Sex determination in humans is a complicated process and one that is still not fully understood. Recently, a region on the short arm of the Y chromosome was sequenced and was postulated to be responsible for determining the testis. This finding was made possible in part by analyzing DNA from both XX and XY individuals having sex reversal. Several questions remain regarding the function of the identified sequence; these involve the interaction between similar sequences on the X chromosome and the identity of the next gene or genes involved in the process of male sexual differentiation.

Generally, all individuals having a Y chromosome will develop a testis regardless of the number of X chromosomes, and individuals lacking a Y chromosome will develop an ovary (Table). However, a variety of clinical situations appear to contradict this general rule. XX males with no obvious Y chromosome develop a normal testis, as do XO males. XY females, often with no obvious chromosomal abnormality, develop ovaries, although these may be streaks. The true hermaphrodite with an XX chromosomal complement may still develop a variety of gonadal structures, including a testis or an ovotestis.

X-Y Interchange in XX Males

XX males appear to have the chromosomes of a normal female, with no obvious Y chromosomal material. The incidence of this condition is approximately 1 in 20,000 males. In 1966, Ferguson-Smith[1] suggested that XX males may be the result of an interchange between the X and the Y chromosomes, which would allow transfer of Y chromosomal material (presumably including the testis-determining region) to the X chromosome. This interchange would have to occur during recombination at meiosis, and so the transfer would be between the paternal X and Y. Page and de la Chapelle[2] demonstrated that most XX males had one maternally derived and one paternally derived X chromosome. Andersson et al,[3] using the technique of in situ hybridization, were able to show that probes detecting Y chromosome short arm sequences clustered on the distal portion of one of the X chromosome short arms. The most terminal band of the X chromosome showed the greatest concentration of the probe, and, significantly, the autosomes were not labeled. Again, these findings suggested that Y DNA was transferred to the short arm of the X chromosome at male meiosis. If the Y chromosome normally contained a testis determining function, then the material translocated to the X chromosome in the XX males should contain the testicular differentiating factor (TDF) gene or genes.

An X-Y interchange of this kind was thought possible because the X and Y chromosomes, at the distal short arm, share a region that regularly combines in male meiosis (the pseudoautosomal region). If recombination extends beyond the pseudoautosomal region, strictly Y-linked sequences could be transferred to the X chromosome. The mechanism might be similar to the well-described X-Y interchange in XXr mice. Several pseudoautosomal loci were mapped, and the TDF region was thought to be very close to the junction of the pseudoautosomal region on the Y chromosome. In fact, the majority of XX males were shown to have paternal pseudoautosomal loci and to have lost specific DNA sequences from the paternally derived distal X chromosome. However, not all XX males had such findings,[4] and Y chromosome mosaicism, or a mutation involving the X or an autosomal chromosome, was also thought possible.

In This Issue

Table. Presence of Y chromosome generally determines testicular differentiation

Exceptions: XX males, XY females

Deletion-Mapping the Y Chromosome

In 1984, Magenis et al[5] demonstrated that a female infant presenting with features of Turner's syndrome had an XY karyotype and gonadoblastomas. High resolution chromosomal studies revealed a deletion of a portion of the Y short arm, with no evidence of mosaicism. This finding provided additional evidence that a gene or genes responsible for male determination was found on the distal half of the Y short arm, as deletion of this small area allowed sex reversal.

Using DNA from 27 individuals[6] (most of them either XX males or XY females with detectable deletions), a deletion map of the Y chromosome was constructed. Before this was possible, cloned Y chromosomal DNA sequences were isolated with the use of DNA libraries or with human-hamster hybrid techniques. The latter technique involved the introduction of a single human chromosome (in this case, the Y chromosome) into hamster chromosomes, thus allowing easier identification of sequences specific for the human Y chromosome.

In this study,[6] the presence or absence of 23 restriction fragments was analyzed. The size and placement of the sequences were ordered to produce a deletion map of the Y chromosome, spanning seven identified intervals. Intervals 1 to 3 were on the short arm of the Y chromosome, interval 4 represented the centromere, and intervals 5 to 7 comprised the long arm of the Y chromosome (Figure 1). The results from the XX males having Y material placed the testis-determining function in interval 1. Interestingly, infertile but phenotypically XY males had deletions on the long arm of the Y chromosome.

Closing In on the Gene

Further work on the XX males and the XY females with deletions allowed interval 1 to be broken down into subregions. Page et al[7] used an XX male with the smallest identified segment of Y DNA and a female with a tY:22 autosomal translocation (and a demonstrated lack of regions 1A2 and 1B) as a starting point to clone the putative testis-determining gene (Figure 2). The gene was cloned by conventional walking methods using the probe closest to the breakpoint of the deleted Y chromosome. In one direction, the investigators hit segments found in common with the XX male; in the other direction, segments in common with the other end of the translocation breakpoint were hit. The deletion thus identified was thought to consist of approximately 120 kilobases, while the entire 1A2 interval was thought to be 140 kilobases, or 1/500 of the Y chromosome.

As the sequenced area was believed likely to contain the testis-determining function, evolutionary conservation was then investigated. DNA from a variety of heterogametic animals was used to make a "Noah's Ark blot." A male-specific band was identified in all animals but chickens.

The identified sequence appeared to represent a long open reading frame and to encode a protein most like transcription factor IIIA from the frog. This transcription factor was known to be a DNA binding protein. The Y encoded protein had a repetitive array of structural elements with zinc fingers. The "fingers" formed a tetrahedral shape around the zinc and were thought possibly to project into the grooves of DNA. Page postulated that the protein had a transcriptional regulatory function and that it was neither a hormone nor a cell surface protein.

Importantly, a similar sequence was found on the short arm of the X chromosome in an area normally inactivated. This raised the question of the function of the X-linked testis-determining region (TDX). Four models were proposed. First, the TDX region was unrelated to the Y-linked testis-determining region (TDY) or to a distinct function. Second, the two regions could cooperate in forming a heterodimer. Third, the X and Y functions could be competitive, perhaps for a common binding site. The fourth and most appealing theory has TDX and TDY being interchangeable, with dosage being of crucial importance. The TDX from one of the two X

Erratum

In the article on occult celiac disease by Asaria Ashkenazi, M.D. (*Growth, Genetics, and Hormones* Volume 5, Number 2, pp 1 to 4), an editing error altered the meaning of one of the author's sentences. The sentence should read: "In recent studies, we demonstrated the toxic effect of purified gliadin-derived peptides on intestinal mucosa cultures of CD patients ingesting a normal gluten-containing diet."

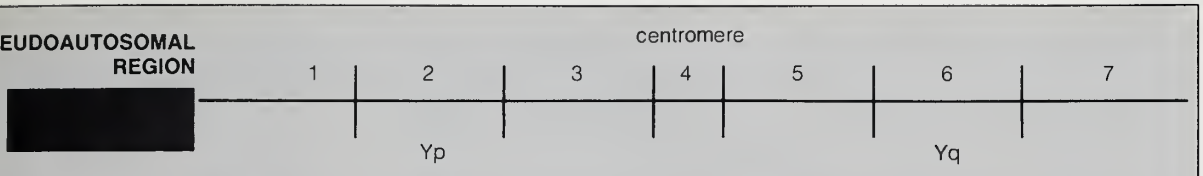

Figure 1 Y chromosome deletion-mapping intervals.

chromosomes of a normal female would normally show inactivation, while the TDX and TDY in a normal male would not show inactivation. In the XX male, the TDY from the X-Y interchange would escape inactivation and allow male development.

New Findings, New Questions

These results were indeed exciting, and they helped explain the clinical findings with sex-reversed individuals. Subsequent work,[8] however, has raised still more questions while providing a few answers. As the Y-encoded protein was not yet proven to be the primary sex determinant signal, its terminology was changed from TDY to zinc finger Y (ZFY). The X-linked gene was correspondingly zinc finger X (ZFX). Interval 1A2 of the Y chromosome was found to contain four restriction fragments of highly conserved sequences, one of which encoded the zinc finger protein. Preliminary evidence suggested that at least two of the other three segments might also be exons of the same gene. These four conserved segments of 1A2 also hybridized to similar segments on the X chromosome. The X-chromosomal counterparts were cloned and compared to the segments from the Y chromosome and were found to be quite similar. Both had a carboxyl-terminal exon encoding the tandem array of zinc fingers with two cysteines and two histidines.

Surprisingly, the transcription of ZFX did not appear to be subject to X inactivation. The level of ZFX's transcription increased with the number of X chromosomes. Other studies demonstrated that the ZFX gene was transcribed whether it was on the "active" or "inactive" X chromosome.

The similar sequential structures

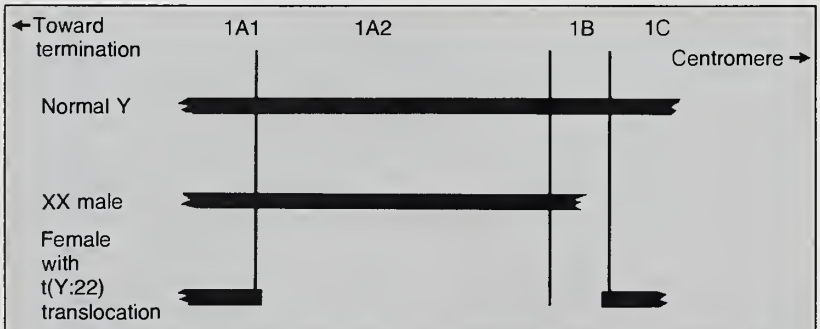

Figure 2 Identifying the locus of the testis-determining gene from breakpoints in the Y chromosome of sex-reversed individuals. The top bar depicts a segment of a normal Y chromosome; the middle bar shows the Y DNA from an XX male; and the bottom bar shows Y chromosome segments (with extensive deletions) from an XY sex-reversed female. The testis-determining gene is believed to lie in a 120-kilobase sequence in the 1A2 region.

of the ZFX and ZFY genes suggest derivation from a common ancestral gene. A possible explanation is that the ancestral gene was initially on a pair of autosomes and may be highly conserved because of evolutionary selective pressure.

The sequence similarity of the zinc finger proteins of ZFX and ZFY also suggests a common nucleic acid binding sequence. While the two gene products could regulate transcription of the same downstream gene, the minor variations between the two genes might also significantly affect binding specificity or affinity.

Another question involves the overall function of ZFY and ZFX. Cultured cells from a variety of human tissues show transcription of the genes and possibly suggest other functions in addition to sex differentiation.

A recent and exciting development has been the demonstration of a Y-linked and closely related X-linked gene transcribing a regulatory protein. The interaction of the two genes is not yet clear, but these could be differentially expressed during embryonic development because of as yet undescribed regulatory mechanisms. Further studies of the expression of these genes in embryos, or analysis of transgenic mice, must be performed to document the sex-determining role of ZFY.

Finally, the role of ZFY in conditions such as Y-negative XX males or XX true hermaphrodites is also unclear.

The importance of clinical observations to the promising developments described here cannot be understated. Continuing collaboration between clinician and basic researcher have over time led to delineation of the crucial steps to testis formation.

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The Final Phase of Growth in Stature

Alex F. Roche, M.D., Ph.D., D.Sc.
Fels Professor
Department of Pediatrics
Wright State University School of Medicine
Dayton, Ohio

Editor's Note

The dilemma of prognosticating how much growth may yet occur after certain milestones of growth are met often frustrates the clinician. A second dilemma of when to stop growth hormone, anavar, estrogen, or other treatment for growth follows from the first. In this article, Dr. Roche addresses these questions and provides some answers. For example, growth in stature ceases in males and females at median ages of 21.2 ± 2.5 years and 17.3 ± 2.5 years, respectively. Children often grow an extra centimeter or slightly more after their growth velocity has decreased to <1.0 cm during the previous year; the later the occurrence of peak height velocity, the later menarche occurs, and subsequent growth in stature after late menarche is less than that in girls with earlier menarche. The reader will find that the abstract entitled, "New Concepts of the Growth Spurt of Puberty," which appeared in the previous issue of Growth, Genetics, and Hormones *(Volume 5, Number 3) will supplement the reading of this article.*

Robert M. Blizzard, M.D.

Knowledge of the "normal" range of growth after particular ages and pubescent events may assist the clinical management of older children with unusual statures. Serial studies are needed to determine the distributions of these growth increments. Partly because the protocols for almost all growth studies cease at 18 years, and partly because marked attrition of the sample population after 17 years is common, there are few reported data concerning the final phase of growth in stature for normal children and almost none for children with pathologic conditions.

The following account summarizes some of the findings from the Fels Longitudinal Study in 1972[1] and presents further analyses of the larger database that is now available from this study. In 1972, data were analyzed for 192 participants aged 28 years or more at their most recent examinations. Data are now available for 520 participants, with serial stature measurements extending to at least 20 years. Many of the Fels participants are siblings or offspring of older participants, and the inclusion of related individuals theoretically could introduce bias. However, the differences between sex-specific analyses in which all the available data were included and those in which only one participant per family was included, are inconsequential. The participants involved in the present analyses were born between 1929 and 1968, but there are no secular trends in these data. Although there was no strict sampling design, distribution statistics for Fels statures are similar to those from national U.S. surveys.

At the time of enrollment, the families of the participants lived in southwestern Ohio. These families were generally of middle socioeconomic status, with distributions of education and occupation that matched those from national samples, except that the lowest group was slightly underrepresented among those born after 1939. All the children were white and healthy.

Stature was measured with a wooden stadiometer until 1971, when a Holtain stadiometer was introduced. Both instruments were calibrated monthly, and the procedures used to measure stature match current recommendations.[2] All measurements were made by two anthropometrists working independently who repeated their measurements when they differed by more than 1.0 cm. The mean inter-observer difference for stature measurements from 12 to 18 years was 0.16 cm (SD 0.15 cm).

Cessation of Growth in Stature

It is difficult to determine when growth in stature ceases. In earlier analyses,[1] a pair of mathematical functions was fitted to the serial data for individuals; the second function was a horizontal line to represent the lack of change during early adulthood. The age at which the fit was maximal for the two functions combined was accepted as the age at which growth in stature ceased. The median ages were 21.2 years for males and 17.3 years for females, with ranges of about 5 years from the 10th to the 90th percentiles.[1] This sex difference in the timing of cessation is greater than that for peak height velocity (PHV) and presumably results from sex-associated differences in growth patterns during the final phase of growth.

Some authors[3] consider adult stature to be reached when an annual growth increment is less than 1.0 cm, but the median increases in stature after such an increment exceed 1 cm in each sex.[1] The data in Table 1 and other findings[4] show that the total median for growth in stature, after an annual increment <1.0 cm, exceeds 1 cm for most age groups. These data demonstrate also that the total growth after an annual increment <1.0 cm was negatively associated with the age at which the low increment occurred. The total increment after four successive 6-month increments, each less than 0.5 cm, is only a few millimeters.[1]

Other investigators contend that adult stature has been reached when maturation of the hand-wrist is complete. After this occurs, however, total increments of 1.6 cm for males and 2.3 cm for females have been reported.[5] In addition, after maturation is complete in both the tibia and femur, the median increases in stature are

1.5 cm for males and 1.0 cm for females.[1] The final phase of growth in stature probably reflects elongation in the vertebral column.

Increments after Peak Height Velocity (PHV) and Menarche

The distributions of the total increments after PHV are slightly larger for boys than for girls, with large differences between the 10th and 90th percentile levels in each sex (Table 2). These sex-associated differences are particularly large for the first year after PHV. The annual increments decrease rapidly after PHV, with almost as much growth in the first year as in the second to fifth years combined. The data for annual increments after PHV do not add up to the total increments, because the groups for the annual increments differ across intervals. It is noteworthy that at least 10% of the boys and of the girls had increments greater than 1.0 cm even from 4 to 5 years after PHV.

The median total stature increment after menarche was 7.4 cm with a 10th to 90th percentile range from 4.3 to 10.6 cm. These findings are in agreement with reports of growth from menarche to the end of school attendance or to 18.25 years.[6,7] The median increments during the first year after menarche exceeded the sum of the median annual increments over the next 4 years.

Relationships to the Timing of PHV and Menarche

The later the occurrence of PHV and menarche, the lesser the growth in stature after these events[1,4,8,9] (Figure). After PHV, there was considerably more growth in boys than in girls for groups matched in age at PHV, but the ranges from the 5th to the 95th percentiles and the slopes of the regressions were almost identical in each sex. The increments in boys from 14 to 17 years are also negatively related to stature at 14 years.[10]

Table 1. Total growth in stature (cm) after an annual increment of less than 1.0 cm

	Percentiles					
Age (years) at increment	Boys			Girls		
<1.0 cm/year	10	50	90	10	50	90
13-14	—	—	—	0.7	1.8	3.3
14-15	—	—	—	0.4	1.4	2.6
15-16	0.4	1.2	1.9	0.2	1.3	2.2
16-17	0.4	1.1	2.4	0	1.1	2.4
17-18	−0.2	0.4	1.6	−0.4	0.0	1.6

Clinical Applications

The preceding data may serve as guides to the potential for growth in stature, depending on the patient's maturational status. This information therefore may assist decisions about the initiation or cessation of therapy. Such decisions will be influenced as well by the presence and nature of any pathological condition and by the attitude of the patient and the patient's family.

More complex procedures utilize regression equations to predict adult stature from childhood variables.[3,11,12] These require assessments of skeletal age and, therefore, cannot be used after maturation of the hand-wrist is complete. Prediction methods based on regression are likely to be misleading when applied to children with chronic diseases that affect growth, with large overpredictions more likely than underpredictions. The Bayley-Pinneau method[13] is the best current procedure for predicting the adult statures of children with diseases; but even with this method, the prediction errors are large.[12] The present data should be applicable to healthy children, including those with statures or maturational levels unusual for their chronological ages.

In making decisions regarding the cessation of growth-promoting therapy, clinicians may utilize the distributions of age at which growth in stature ceases.[1] This approach is limited in value, how-

Table 2. Growth in stature (cm) after peak height velocity (PHV) and menarche

	PHV - Boys			PHV - Girls			Menarche		
Age Intervals	10	50	90	10	50	90	10	50	90
Total	11.6	17.8	23.7	10.8	15.8	22.3	4.3	7.4	10.6
0 to 1.0 years later	5.5	8.0	9.9	5.0	6.9	8.5	1.9	3.9	6.0
1.0 to 2.0 years later	2.9	4.7	6.8	2.0	4.3	6.1	0.6	1.5	3.1
2.0 to 3.0 years later	1.1	2.2	3.5	0.7	1.6	3.5	0.2	0.9	1.7
3.0 to 4.0 years later	0.4	1.0	2.0	0.3	0.9	1.9	0.0	0.5	1.1
4.0 to 5.0 years later	−0.1	0.6	1.5	0.0	0.6	1.1	−0.3	0.3	0.8

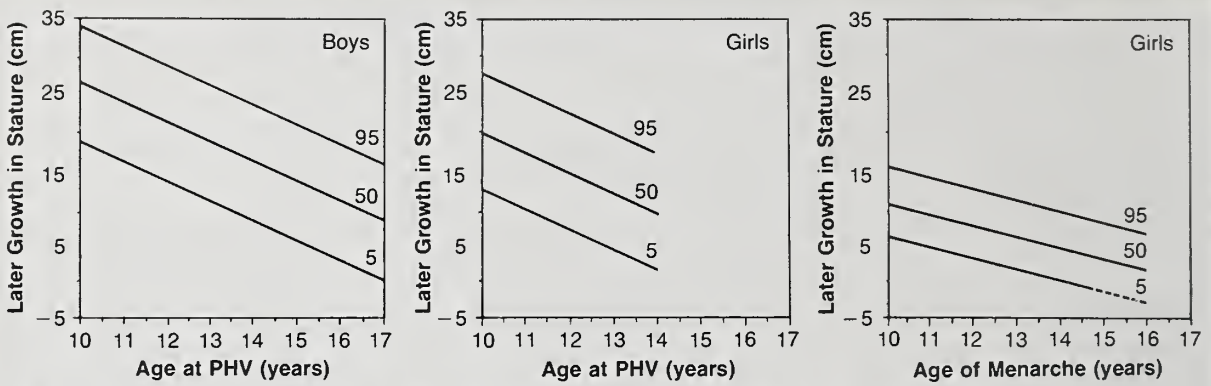

Figure Selected percentiles for the remaining growth in stature (cm) after peak height velocity (PHV) and menarche in relation to the ages at which these events occur. The interrupted portion of the 5th percentile for growth in stature after menarche represents values that are less than zero. These are unacceptable biologically but are found in actual data due to measurement errors.

ever, because growth is very slow prior to cessation, and a decision made on this basis would commonly prolong therapy beyond the age at which it is effective. The present data for expected growth after particular maturational events may offer a more useful alternative for basing clinical judgments. In the absence of an effective stature prediction method for children with diseases, it is recommended that surveillance and treatment continue until about 3 years after PHV or 2 years after menarche. The later these events occur, the shorter the following period during which treatment or surveillance should be continued.

Research Applications

Another major potential application of these data is in study design. If the planned statistical analyses relate to differences in stature increments between experimental and control groups, the present data could assist a power analysis of the sample sizes required. They could also indicate the necessary duration of the study relative to age and maturity levels. If the study is to extend until growth in stature is complete in 90% of the group, data collection must continue until about age 23.5 years in males and 21.1 years in females.[1]

Conclusion

The data discussed here describe late growth in normal children. Presumably, late growth occurs as well in children with chronic diseases, although the magnitude of such changes is likely to be different. Application of these data therefore would require adjustment for the altered rate of growth produced by many diseases. There is, however, insufficient evidence on which to base these adjustments, and further studies are required to provide such support.

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800 Second Avenue
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Address for Correspondence

Please send all correspondence to
Robert M. Blizzard, M.D.
Department of Pediatrics
University of Virginia
School of Medicine
Charlottesville, VA 22908.

Letter from the Editor

This is the 20th issue of *Growth, Genetics, and Hormones,* completing five years of publication. The goals of the Editorial Board have been to assimilate the interests of geneticists, endocrinologists, nutritionists, and pediatricians in respect to the factors that affect growth in children, and to publish articles and abstracts in accordance with these interests. The Editorial Board has received much satisfaction in pursuing its endeavors and expresses its appreciation to Genentech Corporation for the educational grant that has made this publication possible. The Board hopes to continue its efforts in the future; please advise us how we can better accomplish our goals.

For the Editorial Board,
Robert M. Blizzard, M.D.

Special Report:
7th International Symposium on Growth and Growth Disorders

April 21-22, 1989, Rome, Italy

Robert M. Blizzard, M.D.
Chairman
Growth, Genetics, and Hormones

One entire session of this symposium dealt with adult patients with growth hormone deficiency (GHD). Prof. Bjork of Sweden queried 65 adult patients with GHD who were treated with growth hormone (GH) in the past. Twenty-three responded to the questionnaire. There were 47 controls. The conclusion of this inquiry was that patients with GHD were "worse off" than controls with respect to their quality of life. These patients reported that they felt isolated socially, were less active and mobile, had sleep disturbances, and felt less adequate emotionally than the controls. The data suggested that a significant proportion of patients with GHD have psychological damage from their chronic disease. Several individuals from the audience suggested that the control group should not have consisted of normal individuals, but individuals with other types of chronic illness or patients with short stature who were not growth hormone deficient. The various discussants agreed that the GHD patients were handicapped, but there was no way to know how they compared to individuals with other handicaps.

Drs. O.M. Rutherford and M. Preece of London reported changes in skeletal muscle after discontinuing GH in GHD patients. The study was established because a significant decrease in the cross section of the thigh, as determined by CT scan, was noticed in one patient with GHD who had stopped GH treatment upon becoming an adult. In this study 7 of 8 patients who stopped GH because they were late adolescents or adults experienced decreases in muscle strength and size of the quadriceps. Biopsy demonstrated that the fiber area of the quadriceps was decreased. Interestingly, only one of the subjects was found to have a decrease in triceps area, and no change in strength was found in this muscle.

Drs. H. Whitehead and D. Hadden of Belfast looked at muscle fiber size in 13 GHD patients 19 to 52 years of age. Seven had been treated with GH, but not for at least 6 months before the study was undertaken. In these patients, GH was adequately replaced with hydrocortisone, thyroxine, and sex steroids. The study was of a double-blind crossover design, in which subjects received GH, 0.5 U/kg/wk divided into daily injections, for 6 months. Eleven of the 13 completed the study. The data from biopsies indicated that 6 months of treatment had no effect on the size or the type of muscle fibers. The authors emphasized that this was a small population.

Prof. Sonksen of London then discussed the effects of 6 months of GH treatment on body composition in adults with GHD. Twelve subjects received placebo and 12 received GH. Their average age was 30 ± 3 years. Studies included body composition (assessing total body potassium), a CT scan of the thigh, and measurement of various chemical parameters. The results indicated that the lean body mass increased, but fat mass decreased significantly. The fat area in the thigh did not change, but the skin fold thickness decreased by 25%; this decrease was most marked in the abdominal area.

Dr. G. McGauley of London assessed the quality of life before and after GH treatment in adults with GHD. Seventeen GHD patients who received GH were compared to 17 who did not. The former perceived that they incurred less illness and had a better quality of life. The actual measurements of differences were minimal, however.

Prof. J.M. Connor of Glasgow presented an excellent discussion of the molecular genetics of Turner's syndrome. "We must consider DNA analysis as well as chromosome analysis in patients with Turner's syndrome," he stated. Connor reported an interesting observation that in all 14 cases tested, the X chromosome came from the mother. Connor

emphasized that DNA analysis can pick up translocations and that Y material can occur in individuals with XO/XX syndrome. In such individuals gonadectomy is indicated. Y determinants should be looked for in all XO/XX Turner's patients, and this can best be done by DNA probes. Connor stated that 10% of XO/XX girls have unexpected chromosome material. He also noted that 2% of all pregnancies start with 45 XO chromosome karyotype and that the majority of these abort spontaneously.

Prof. R. Rappaport of Paris discussed the theories of growth retardation in patients with Turner's syndrome. The endocrine hypothesis—ie, GHD—was considered first. He carefully reviewed the data from the literature, which he agreed is confusing. He emphasized that complete GHD is rare and explained that the differences in data from various clinics may be related to the fact that GH production is not the same at various stages of preadolescent life, and various investigators have reported on patients of varying ages. Values of integrated GH concentrations in patients with Turner's syndrome must be compared with those of normal preadolescents, as GH production increases in puberty. Rappaport believes that GHD is *not* significant in patients with Turner's syndrome. Furthermore, patients with Turner's syndrome do not respond as well to GH therapy as do GHD patients, and this mitigates against the possible diagnosis of GHD. He then considered the possibility of a chromosomal defect and stated that the genes on the short arm of X and Y are believed to be genes accounting for stature. Absence of these genes will produce short stature. Rappaport also talked about the likelihood of these patients having a primary skeletal defect. He presented histological data collected several years ago by Dr. Scinescu regarding the growth plate cartilage of patients with Turner's syndrome. Clusters of chondrocytes were found in such patients, and there was abnormal organization of cartilage. In the discussion session that followed, Prof. Bierich of West Germany reported testing 36 patients with Turner's syndrome for integrated concentrations of GH. Several had decreased GH production compared to normals.

Prof. A. Ferrandez of Spain and Dr. R. Rosenfeld of Stanford (USA) then discussed studies of GH therapy in patients with Turner's syndrome. Ferrandez reported that patients receiving GH, GH plus anavar, or GH plus estrogen in small doses had an increase in the cortical thickness of bone and no change in bone age. There also were increases in bone density and in growth. Skin folds decreased in all groups. Dr. Rosenfeld reported on 4 years of collaborative experience with the Genentech DNA recombinant growth hormone. The summation was that patients with Turner's syndrome receiving GH plus anavar, or even GH alone, are now exceeding the heights projected at the time they began GH therapy.

This conference focused on adult patients with GHD and on patients with Turner's syndrome. Our understanding of Turner's syndrome is now at the point where such patients possibly should have the opportunity to receive GH as a therapeutic agent. However, we will need more information concerning GH production in normal adults before we can conclude that GH is also good therapy for adults with GHD.

Meet the Editorial Board

Associate Editor
Jean-Claude Job, M.D.

Dr. Job is Professor and Chairman of Pediatrics at the Hôpital Saint-Vincent de Paul in Paris. He also heads the pediatric clinic, in which he organized a division of endocrinology.

A leading investigator of biosynthetic human growth hormones in France, Dr. Job developed a research laboratory on human growth under the auspices of the French national institute of health, INSERM, and has served as research director since 1978. He organized the French national committee for hGH (France-Hypophyse), which he served first as secretary and, since 1983, as president. He also established a working group on hGH for the European Society of Pediatric Endocrinology.

Dr. Job earned his medical degree from the University of Paris in 1952. He has published more than 450 papers in French and international medical journals and is the editor of a textbook on pediatric endocrinology.

Dr. Job is a member of the European Society for Pediatric Endocrinology, the Société Francaise de Pédiatrie, and the Société Francaise d'Endocrinologie. He is also a corresponding member of the Lawson Wilkins Pediatric Society.

Special Report

The American Diabetes Association Scientific Meeting

June 3-6, 1989, Detroit, Michigan

William L. Clarke, M.D.
Associate Editor
Growth, Genetics, and Hormones

Several of the presentations at this meeting may be of interest to readers of *Growth, Genetics, and Hormones*. Geneticists, in particular, will be interested in the symposium on "New Developments in Immunology and Genetics of Insulin-Dependent Diabetes Mellitus [IDDM]," which included a talk by John I. Bell (Oxford, England) entitled, "Genetics of Insulin-Dependent Diabetes Mellitus—Has a Susceptibility Gene Been Found?" Dr. Bell described the epidemiologic and laboratory studies that have led to the identification of the association between the amino acid at position 57 of the human leukocyte antigen-DQ (HLA-DQ) beta chain and IDDM susceptibility in whites. The hypothesis is that aspartic acid (Asp) at position 57 protects against IDDM.

Dorman and Trucco (*Diabetes* 1989;38[2]:34A) reported on the contribution of the HLA-DQ phenotype to the incidence of IDDM in Allegheny County, Pennsylvania. Their previous studies demonstrated that the relative risk of developing IDDM for individuals homozygous for lack of Asp at position 57 of the DQ beta chain, compared to those with at least one DQ gene with Asp, was 107. The incidence of IDDM for non-Asp homozygotes was calculated to be 74 per 100,000, and for those with at least one Asp allele it was 0.69 per 100,000. The annual incidence attributable to the phenotype was thus 73.3 per 100,000. They then calculated the population attributable fraction to be 95%. The non-Asp/non-Asp phenotype is therefore a major determinant of the incidence of IDDM in Allegheny County, Pennsylvania. Trucco et al (*Diabetes* 1989;38[2]:19A) described a relatively simple and quick test that within 24 hours can detect the presence or absence of Asp-57 without using either allele-specific oligonucleotide probes or radioactive probes. Ikegami et al (*Diabetes* 1989;38[2]:19A) analyzed HLA-DQ beta chain sequences in Japanese patients and determined that the DQ beta characteristics in Japanese IDDM patients are different from those in white populations, and that the DQ-alpha and/or DR sequence also may affect susceptibility.

Presentations regarding the relationship of growth hormone and diabetic retinopathy also were of interest. Rymaszewski et al (*Diabetes* 1989;38[2]:30A) studied the response of retinal capillary endothelial cells of humans in vitro to human growth hormone (hGH) stimulation. They determined, using long-term cultures of retinal endothelial cells from normal, postmortem human eyes, that exposure to hGH (200 ng/mL x 4 days) after the second passage in the presence of 10% horse serum, resulted in a 55 ± 9% greater cell number versus controls. Tritiated thymidine incorporation was stimulated at hGH concentrations as low as 1.2 ng/mL. Thus, physiologic concentrations of hGH stimulated mitotic activity of highly purified human retinal capillary endothelial cells. These studies suggest a direct responsiveness of the retinal endothelium to hGH. Dills et al (*Diabetes* 1989;38[2]:5A) measured insulin-like growth factor I (IGF-I) serum levels in 876 subjects with diabetes diagnosed at 30 years of age or older. Proliferative retinopathy was found in 15.6% of the insulin-taking population (N = 488). After controlling for duration of diabetes, glycosylated hemoglobin, blood pressure, proteinuria, and age at diagnosis, higher levels of IGF-I were associated with an increased risk of proliferative retinopathy in those subjects taking insulin. The authors suggest that high IGF-I levels may be a factor for the development of proliferative retinopathy. Grant et al (*Diabetes* 1989;38[2]:56A) measured vitreous concentrations of IGF-I and -II by radioimmunoassay in 40 subjects with retinopathy and 18 nondiabetic subjects. Seventy-two percent of the diabetic subjects had vitreous concentrations of IGF-I capable of inducing increases in chemotaxis of human retinal endothelial cells (>5.0 ng/mL). IGF-II concentrations in the vitreous exhibited a distribution similar to IGF-I levels, and the concentrations of both correlated moderately with their serum concentrations.

Horber and Haymond (*Diabetes* 1989;38[2]:56A) studied the insulin resistance induced by hGH and prednisone in nondiabetic subjects. Glucose and leucine oxidation after an 18-hour fast, and during gut infusion of glucose and amino acids, was measured. Subjects were studied after 7 days of placebo, hGH 0.1 mg/kg/day, prednisone 0.8 mg/kg/day, or hGH plus prednisone. Fasting glucose was similar during the placebo and hGH administration, but was elevated during prednisone administration and during the combination of hGH and prednisone. Leucine oxidation was increased by prednisone but decreased by hGH administration and unchanged during combined treatment. By indirect calorimetry, glucose oxidation was similar in all groups. Insulin levels were higher during combined therapy than during placebo, hGH, or prednisone treatment. In summary, the insulin resistance of hGH and prednisone was demonstrated to be additive. The authors concluded that the insulin resistance of hGH and of prednisone may be caused by independent mechanisms. Prednisone decreased fat oxidation and increased leucine oxidation, whereas hGH treatment did the opposite. hGH and prednisone may reciprocally regulate oxidation of protein and fat, while decreasing the efficiency of glucose disposal.

Variation in Lower Leg Growth With Alternate-Day Steroid Treatment

The growth of a boy with Crohn's disease was studied intensively over 4 weeks. Lower leg length was measured with a knemometer (mean of four measurements) every day (except for weekends). The standing height was measured weekly. The subject was 11.6 years old and had had the disease for 5 years. He was on a regimen of 1 g of sulfasalazine twice daily and 7.5 mg soluble prednisolone on alternate days (taken after the measurement session, which was 1 hour after arriving on the ward). In the fourth week the steroid was put "out of phase" by 1 day, to see if the pattern of growth reversed.

A clear distribution of leg-length gains was shown. Despite some overlap, a highly significant difference was demonstrated between the means of the steroid days and those of the steroid abstinence days. Growth on the days of steroid ingestion was fractionally below zero, but the gain on the days the patient was off steroid averaged 0.5 mm ($t = 3.6$). Soft tissue changes at the knee and heel were measured by ultrasound, but no consistent change was noted.

Wales JKH, Milner RDG. *Arch Dis Child* 1988;63:981-983.

Editor's comment—*This report is important in showing exactly what the knemometer does best: measuring short-term growth changes in the context of physiologic or pharmacologic investigations of the growth plate, or of factors affecting it. It provides direct evidence of the expected inhibiting effect of high doses of steroid on growth, followed by catch-up as soon as the steroid is removed.*

James Tanner, M.D.

The Role of the Vitamin D Endocrine System in Health and Disease

Vitamin D is not only a vitamin, but also a hormone. $1,25(OH)_2D3$ and $1,25(OH)_2D2$ are the principal vitamin D mediators that regulate bone and mineral metabolism in humans. There are, however, other actions of $1,25(OH)_2D3$—and probably $1,25(OH)_2D2$—that have not been well recognized by practitioners. This article reviews current concepts in this field.

The circulating 25(OH)D3 level reflects the availability of vitamin D3 and is thought to be the best indicator of vitamin D levels. Feedback mechanisms play pertinent roles, as they do in the other endocrine systems. For example, $1,25(OH)_2D3$ decreases the level of 25(OH)D3. $1,25(OH)_2D3$ in excess also decreases its own level by shifting the synthesis of 25(OH)D3 to $24,25(OH)_2D3$ instead of continuing to synthesize $1,25(OH)_2D3$.

Other factors regulating the synthesis of $1,25(OH)_2D3$ include parathyroid hormone (PTH), which stimulates 1α-hydroxylase activity, as do low dietary phosphate and hypophosphatemia. Hyperphosphatemia, in contrast to hypophosphatemia, decreases 1α-hydroxylation. Several other hormones secondarily affect $1,25(OH)_2D3$ levels. Estrogen, for example, increases $1,25(OH)_2D3$ because vitamin D binding protein is increased.

Synthesis of $1,25(OH)_2D3$ occurs to some extent in organs other than the kidney, eg, in patients with sarcoidosis who are anephric. Ectopic synthesis also occurs during pregnancy, as placental and decidual cells produce the hormone.

Substantial evidence has accumulated that the mechanism of action of $1,25(OH)_2D3$ is similar to that of other steroid hormones, in that the hormone-receptor complex is associated with DNA in the nucleus. Here it either initiates the synthesis of specific RNA encoding proteins or mediates a selective repression of gene transcription. The $1,25(OH)_2D3$ receptor protein is expressed in almost every tissue examined so far.

With respect to calcium metabolism, $1,25(OH)_2D3$, in concert with PTH and calcitonin (CT), acts on bone, intestine, and kidney. $1,25(OH)_2D3$ plays a role in the regulation of osteoblast function, although its effect on bone growth and mineralization is probably not mediated directly via osteoblasts. As for osteoclast activity, which contributes to bone resorption: administration of $1,25(OH)_2D3$ increases the number of osteoclasts found in rats.

In the parathyroid gland $1,25(OH)_2D3$ decreases PTH release by increasing serum calcium and by a direct short-loop feedback message that inhibits the synthesis of PTH through an interaction with the prepro-PTH gene. In the intestine, it stimulates the influx of calcium and phosphorus from the lumen through the intestinal wall and into the plasma. For calcium, this is done by activating an increased production of calbindin-D in the intestinal wall which, in turn, enhances calcium absorption.

The authors also discuss at length the role of $1,25(OH)_2D3$ in involutional osteoporosis, rickets, granulomatous diseases, cellular growth and differentiation, interaction with the hematopoietic system, effects on lymphocytes, and interaction with cancer cells.

Reichel H, Koeffler HP, Norman AW. *N Engl J Med* 1989;320:980.

Editor's comment—*This is a lengthy and excellent review of the contributions of vitamin D to both normal and pathologic conditions. The data and concepts are up to date. Readers interested in the details of vitamin D metabolism are encouraged to use this article as a reference.*

Robert M. Blizzard, M.D.

Growth Failure: A Complication of Dietary Treatment of Hypercholesterolemia

A group of 40 children were advised to pursue a low-cholesterol and low-fat diet because of relative or unequivocal hypercholesterolemia. Few studies evaluating the benefits and risks of dietary recommendations to children with hypercholesterolemia have been reported. Thirty-two of the patients were considered to have normal growth, although some were seen relatively shortly after the diagnosis was made and treatment was initiated. The remaining 8 were considered to have growth failure associated with the dietary treatment. Three had growth inhibition primarily of height and 5 primarily of weight. The 8 patients were ingesting approximately 65% of the calories necessary for energy expenditure and approximately 40% of the dietary requirement for zinc. The 3 patients with growth inhibition of stature were obtaining only 20% of their energy expenditure through fat ingestion and consumed even less calories than the other 5 (<60% of the established energy requirement for their ideal weight, sex, and age).

The authors comment that these data demonstrate that the diagnosis and unsupervised dietary treatment of hypercholesterolemia in children may have adverse consequences. In this study a high proportion of patients who were advised to eat a low-fat, low-cholesterol diet because of hypercholesterolemia consumed diets inappropriate to sustain normal growth and weight gain and to initiate pubertal development. The diets consumed by those with growth failure were mainly inadequate in energy and zinc. The authors conclude that a reduction in fat intake to less than 30% of total energy may not be routinely warranted in children with hypercholesterolemia and that such restrictions should be reserved for those who fail to reduce their serum cholesterol levels when following a prudent diet. Sufficient dairy products, red meat, and eggs to meet nutritional standards should be included in the diet, and this can be done without increasing the fat and cholesterol intake beyond the aforementioned guidelines. These recommendations are in accord with those of the Committee on Nutrition of the American Academy of Pediatrics, who concluded in their report that any restrictions on dietary patterns during the first 20 years of life should be viewed with caution. The authors strongly recommend assistance from a dietitian or nutritionist when planning diets for children with hypercholesterolemia.

Lifshitz F, Moses N. *Am J Dis Child* 1989;143:537-542.

Editor's comment—*I can only reemphasize the comments made by Dr. Laurence Finberg, in an editorial entitled "Dietary Advice: Responsibility for Monitoring" that appeared in the* American Journal of Diseases of Children. *Dr. Finberg noted that the dietary requirements of children differ from those of adults in many respects, eg, children need more calories for energy and a variety of nutrients at higher levels to promote optimal growth. Finberg agreed that a prudent diet in the presence of hypercholesterolemia was indicated for the patients reported here. In the 20% of patients (8/40) with growth retardation, the failure lay in the monitoring of growth and in the provision of advice concerning the intake of all necessary nutrients.*

Robert M. Blizzard, M.D.

Growth and Endocrine Disorders Secondary to Cranial Irradiation

Rappaport and Brauner present data from the literature and their own studies concerning cranial and spinal irradiation therapy and its effect on growth and pubertal development. Of a group of children given 2,400 rad as prophylactic irradiation for acute lymphoblastic leukemia, 56% had growth hormone (GH) deficiency with a peak GH response to arginine-insulin of <8 ng/mL. Complete GH deficiency (two consecutive GH peak responses <5 ng/mL) was observed in 30% of the same population. Eight children treated with 1,800 rad had normal GH responses at least 4 years after radiation. In addition, normal GH secretion was found in a group of children treated for retinoblastoma who received <2,000 rad. All children who received >4,500 rad for optic glioma had GH deficiency. Younger children were reported to be more vulnerable to the effects of radiation than older children or adults. In addition, the timing of the occurrence of GH deficiency was reported to be related to the radiation dose. GH deficiencies may appear during the first year after radiation in patients receiving more than 4,500 rad, and most of these children are GH deficient within 2 to 3 years. In the authors' experience, GH deficiency will almost always appear within 5 years of radiation, and no affected child has resumed GH secretion. The authors also discussed the use of different stimulation tests, plasma insulin-like growth factor I values, and possible mechanisms for GH deficiency.

Pubertal development also was discussed. Five of 45 children treated with 2,500 to 5,000 rad before or during puberty showed complete gonadotropin deficiency at pubertal ages, while two children had partial gonadotropin deficiency. Diabetes insipidus has not been reported after cranial irradiation and hypothyroidism is infrequent.

Growth after cranial irradiation was dose dependent. Radiation doses in excess of 3,000 rad will

reduce final height in most children, whereas low-dose cranial irradiation (1,800 to 2,400 rad) produces variable responses. Spinal irradiation may have an effect on sitting height that is independent of GH deficiency and that results from decreased growth of the spine.

The final section of this report deals with GH therapy in cranial-irradiated children. Although patients initially have catch-up growth, the authors' data (unpublished) confirm that prolonged GH therapy does not significantly improve the mean height SDs of patients given cranial and/or spinal irradiation. The possible reasons for this include 1) a shorter duration of GH deficiency, 2) a less retarded bone age at the onset of GH therapy, 3) a lower initial (first year) growth velocity response, and 4) the presence of early puberty, which had accelerated bone age faster than the growth velocity. Despite these less than optimal responses, the authors state that it is essential to begin GH therapy as soon as growth velocity declines and radiation therapy has been concluded. They consider treating any child with a height loss of 1 SD or more who has proven GH deficiency. The follow-up period after radiation must be 2 years or more.

Rappaport R, Brauner R. *Pediatr Res* 1989;25(6):561-567.

Editor's comment—*This paper presents few new data, but it is a good review of the effects of cranial spinal irradiation on GH secretion and pubertal development. As such, it is quite comprehensive and deserving of close scrutiny.*

William L. Clarke, M.D.

Puberty in the Syndrome of Septo-optic Dysplasia

Hanna et al retrospectively evaluated pubertal development in 13 patients with septo-optic dysplasia. The patients were grouped according to the timing of puberty. Six of the 13 patients comprised group 1; they had clinical signs of puberty beginning earlier than anticipated (bone age <10.5 years in girls, <11.5 years in boys) and experienced rapid progression of puberty associated with bone ages advancing more rapidly than chronologic age. Growth rates were normal-to-increased in this group, but because of the rapid advancement in bone age, these patients lost growth potential. Three of the 13 patients were classified in group 2, with puberty beginning at the expected time and the progression of puberty considered to be normal. The remaining four patients (group 3) were judged to be gonadotropin deficient by low serum levels of follicle-stimulating hormone and luteinizing hormone at bone ages of 12 years in the three girls and 13 years in the boy. Minimal signs of puberty were present at a mean chronologic/bone age of 16.8/13.7 in the girls and 17/13 in the boy, and replacement therapy with sex steroids was instituted.

The authors comment that sexual precocity in girls with septo-optic dysplasia has been described previously. However, they note that precocity affects boys as well as girls, is most often associated with isolated GH deficiency, and is independent of visual limitation.

Hanna CE, Mandel SH, LaFranchi SH. *Am J Dis Child* 1989;143: 186-189.

Editor's comment—*Although this report is a retrospective study, its contributions are important. Twelve of the 13 patients reported in this study received growth hormone therapy. However, only four of these (group 3) had multiple hormonal deficiencies and significant pubertal delay or absence. The others either had normal progression of puberty or sexual precocity. Despite the high percentage of patients with abnormal puberty, it is important to note that not all patients with septo-optic dysplasia experience abnormalities of pubertal timing and progression. Thus, it is not possible at this time to make predictions concerning puberty in those children who do not have multiple hormonal deficiencies.*

William L. Clarke, M.D.

Birth Prevalence of Skeletal Dysplasias

The prevalence of skeletal dysplasias at birth has received relatively little attention, and the completeness of the available data has been viewed with concern. Two recently reported prospective, population-based studies shed light on this subject.

Stoll and colleagues examined birth records, roentgenographic reports, autopsy reports, follow-up pediatrician notes, and other available data from 11 maternity hospitals where all births were recorded from Strasbourg, France and the surrounding region, from 1979 to 1986. The data from fetuses delivered with a minimum age of 20 weeks and from pregnancies interrupted following prenatal diagnosis of a skeletal dysplasia were included; ascertainment was thought to be complete. A skeletal dysplasia was diagnosed in 34 cases out of 105,374 births to give a prevalence rate of 32.2 per 100,000. The rates per 100,000 births for several of the more common disorders were: achondroplasia, 6.4; thanatophoric dysplasia, 2.8; achondrogenesis, 2.8; osteogenesis imperfecta, 6.4; osteoperosis, 1.8; and multiple exostoses, 1.8. Roughly half of the patients had disorders that are usually lethal in the newborn period.

The second study, by Andersen, examined the birth prevalence of lethal bone dysplasias. Clinical and radiographic findings were analyzed from all births, including stillbirths, in the county of Fyn, Denmark, from 1970 to 1983. Twelve

Limb Lengthening by Epiphyseal Distraction in Chondrodystrophic Bone: An Experimental Study in the Canine Femur

Distraction of the left distal femoral epiphysis was carried out in 18 chondrodystrophic dogs at 19 to 22 weeks, an age comparable to early adolescence in humans. The distraction rate was 0.5 mm/day. Epiphysiolysis occurred after 4 to 9 days, and the treatment was continued for 3 weeks. The average gain in length (measured on radiographs at cessation of treatment), compared to the contralateral control side, was 1.4 ± 0.3 cm. At 2 weeks callus appeared in the gap of the lengthening zone. Osteogenic activity was most distinct at the metaphyseal side. Periosteal reaction along the diaphysis produced widening of the diaphyseal diameter. After removal of the pins, the distracted zone appeared as radiodense immature bone, which soon became mature. Closure of the distal epiphyses took place at about 8 months on the operated side and 9 months on the other.

Animals were killed 3 weeks after cessation of distraction (group 1, n = 5), at 19 weeks (group 2, n = 10), or 71 weeks (group 3, n = 3). At postmortem, femoral lengthening in group 1 was confirmed at 1.2 cm (12.3% of metaphyseal length); in groups 2 and 3, observed after leg growth had ceased, the gain was 0.7 cm (6.1%). That is, there was a loss of residual growth potential in the distracted epiphysis. The torsional strength of the distracted femur ranged from 83% (group 1) to 98% (group 2) to 107% (group 3) of that of the contralateral control. Degenerative changes in the knee joint were observed in three animals in each group.

In conclusion, lengthening by epiphyseal distraction of the distal femur of chondrodystrophic dogs resulted in reduction of residual growth in the involved growth plate. This finding is in accordance with what we previously have observed in analogous studies of animals with normal growth. The procedure obviously had an adverse effect on the growth plate. It is unlikely that the situation would be different in humans. The observed retardation effect on the traumatized growth plate is a sequela that, in general, restricts the use of epiphyseal distraction to the late adolescent period when residual growth is negligible. In successive bilateral lengthening of multiple bone segments by epiphyseal distraction, a procedure that requires an early onset of lengthening, retardation of residual growth may cause significant reduction of gained length. The development of degenerative joint changes is a potential risk that probably does not legitimate epiphyseal distraction as the method of choice in the femur.

Fjeld TO, Steen H. *J Orthop Res* 1989;7:184-191.

Editor's comment—*With the increasing demand for leg-lengthening operations, basic studies such as this one are very much needed. Its findings are clear and unequivocal. At least in dogs (and also in goats, according to an earlier report), epiphysiolysis damages the growth potential of the split-off growth plate—a not unexpected finding. This seems to restrict the technique to late adolescence, when, unfortunately, less growth potential remains.*

James M. Tanner, M.D.

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lethal bone dysplasias were diagnosed out of 77,977 total births to give a prevalence of 15.4 per 100,000. Three cases of thanatophoric dysplasia (including one with cloverleaf skull) and five cases of achondrogenesis type II were identified, yielding respective prevalence values of 3.8 and 6.4 per 100,000 births, respectively.

Stoll C, Dott B, Roth M-P, et al. *Clin Genet* 1989;35:88-92.
Anderson PE. *Am J Med Genet* 1989;32:484-489.

Editor's comment—*These reports provide relatively similar birth prevalence rates for skeletal dysplasias when one takes into account that the study by Stoll and colleagues examined both lethal and nonlethal conditions whereas Andersen looked only at lethal disorders. Together the data suggest that the prevalence of all skeletal dysplasias is slightly greater than 30 per 100,000 births, of which approximately half are lethal in the perinatal period. This figure translates into a rate of around 1 per 3,000 births. This rate, which is actually an underestimate as many disorders are not evident at birth, is much higher than is generally appreciated. For comparison, approximate prevalence rates for several well-known genetic conditions are as follows: Down syndrome, 1 per 700 births; cystic fibrosis, 1 per 1,600 births; muscular dystrophy, 1 per 3,500 male births; hemophilia, 1 per 5,000 male births; phenylketonuria, 1 per 15,000 births; and albinism, 1 per 40,000 births.*

William A. Horton, M.D.

In Future Issues

Inflammatory Bowel Disease and Growth Retardation
by Richard Grand, M.D.

IGF-Binding Proteins: Their Physiological and Clinical Importance
by Michael Ranke, M.D.

Genomic Imprinting
by Judith G. Hall, M.D.

How Bones Grow
by William A. Horton, M.D.

Paracrine Aspects of Bone Metabolism
by David Baylink, M.D.

Surgically Curable Hypophosphatemic Rickets

All patients with apparent hypophosphatemic rickets (HR) do not have an inherited defect. A small but significant proportion have a tumor, which results in a very similar clinical picture. The history of one such patient and a review of the literature comprise the contents of this article.

An 8-year-old boy with rickets had swollen wrists for 6 months and knee pain for 30 months. His height had continued between the 25th and 50th percentiles. The only physical findings were tenderness and swelling of the wrists and right knee and genu valgum.

The findings were consistent with the proposed diagnosis of HR. Roentgenography confirmed the diagnosis. Demineralization of the pelvis, an occurrence seen in severe rickets, was present. A large lytic 6 x 2.5 cm lesion with sclerotic borders was noted at mid-femur on the right.

Following treatment with calcitriol (1.5 μg/day) and Neutra-Phos, a phosphorus replacement supplement (0.5 g three times daily), for 4 months the rickets improved. After discontinuing treatment for 2 weeks the lytic lesion was surgically removed. Within 15 days postoperation, serum phosphorus rose to normal levels. The patient was cured as evaluated by chemical analysis of serum and urine. The histopathology of the tumor was consistent with a diagnosis of hemangiopericytoma.

Only six other cases of HR associated with bone tumors in children have been reported in the literature. The tumors were classified as fibrous dysplasia, fibroma, osteoblastoma-like variants, and non-osseous soft tissue tumors. In adults, HR occurs with connective tissue tumors located in soft tissues that have morphologic features of hemangiopericytoma.

The authors conclude that the tumor produced a phosphaturic substance that impaired phosphate resorption by kidney tubule cells, although production of a substance inhibiting vitamin D metabolism has been implicated in other cases. In this patient, an associated amino aciduria was of diagnostic import in distinguishing genetic from tumor-caused etiology. Most importantly, the authors urge that the possibility of a tumor be considered in sporadic cases of HR.

Hanukoglu A, Chalew SA, Sun CJ, et al. *Clin Pediatr* 1989;28: 321-325.

Editor's comment—*The diagnosis of tumor could readily be missed in sporadic cases of HR. The presence of amino aciduria is found in vitamin D deficiency and vitamin D dependency rickets but not in HR unless a tumor is present. Although most physicians probably do not check for amino aciduria, the presence of this substance should be evaluated in all sporadic cases. If found, screening for tumor should follow. The absence of amino aciduria may not absolutely exclude the possibility of tumor, but it makes it much less likely.*

Robert M. Blizzard, M.D.

Management of Idiopathic GH-Deficient Patients During Puberty

At the Fifth International Symposium Regarding Growth and Growth Disorders, Berlin, April 1988, Price et al presented data from their clinic and from the literature regarding the growth of patients with growth hormone deficiency (GHD) during spontaneous or induced puberty. Boys with idiopathic GHD had a significantly later onset of puberty (15.0 to 15.9 years) than normal boys (11.5 to 12.0 years). The peak height velocity (PHV) occurred at 16.0 to 16.4 years, compared with 14 years in normal boys. The bone ages were comparable (13.5 to 14.0 years) at the time of PHV in the two groups. The PHV was less in the GHD group and the total gain after G2 sex development was 17.0 to 22.8 cm (means of four groups of GHD patients studied at different centers) vs 27.4 cm in normals and 18.0 cm in boys with constitutional delayed growth (CDG). The loss in final height SD score (-2 to -2.5) may reflect pretreatment loss rather than a failure of adequate treatment during puberty, because the total gain after G2 sex development was comparable to that of boys with CDG. The GH treatment was unsophisticated by modern methods, with fixed doses independent of body size given two to three times per week. Data regarding girls were very limited and, therefore, are not reported here.

With respect to treatment, the authors did not encourage an increased dose of GH during puberty because significantly increased growth velocity occurs spontaneously in boys with isolated GHD and because of the greater cost of larger doses. They urged, however, that daily rather than intermittent doses be used. They also stated the need for further information before dose schedules for pubertal patients can be firmly recommended.

Manipulation of puberty was recommended in patients who have GHD and either gonadotropin deficiency or sexual precocity. In the former, the authors recommended strongly that physicians consider the induction of puberty at 14 to 15 years of age in boys and 13 to 14 years of age in girls. They also suggested that this approach be considered in patients with isolated GHD if puberty has not developed spontaneously. Their ar-

guments are based on the psychological need of adolescents to develop at these chronologic ages and the disproportionate stature that develops if treatment is prolonged. Six boys with luteinizing hormone deficiency who were not treated with testosterone until late had an SD score for mean leg length/sitting height of 1.4, compared with 0.6 in isolated GHD. Low doses of testosterone (25 mg twice monthly) are advised in boys to counteract the shorter pubertal duration of 2.7 vs 4.2 years observed when 100 mg was given monthly. Estrogen, 2 to 5 μg/d, was recommended for girls. The authors suggested that delay of puberty with gonadotropin-releasing hormone analogs should be considered in patients with sexual precocity, but they readily admit that data are not available to evaluate the effectiveness of delaying epiphyseal fusion in order to increase height.

Price DA, Shaleta SM, Clayton PE. *Acta Paediatr Scand* 1988;347 (suppl):44-51.

Editor's comment—*The fact that testosterone, endogenous or exogenous, stimulates growth in GH-deficient patients, and that Laron dwarfs have an adolescent growth spurt, support the concept that the growth spurt at adolescence is derived, at least in part, from a direct action of testosterone on the growth plate. The second, and possibly more influential, action is via the increased GH secretion that occurs under the influence of testosterone. Whether additional GH should be given to GH-deficient patients while they are passing through adolescence is still debatable. Each case should be individualized, and the decision to treat should be made on the basis of current height, bone age, mid-parental height, and cost. Some very short GH-deficient patients certainly should be given the opportunity to grow maximally while passing through adolescence and should be considered for additional GH treatment.*

Robert M. Blizzard, M.D.

Urea Synthesis, Nitrogen Balance, and Glucose Turnover in Growth-Hormone-Deficient Children Before and After Growth Hormone Administration

Dahms et al studied urea synthesis and glucose turnover using a primed constant infusion of $^{15}N_2$-labeled urea and a constant infusion of [6,6-$^2H_2$]glucose in 10 prepubertal, growth hormone (GH)-deficient children prior to and after 6 days of human GH (hGH) therapy. The patients were admitted following diagnosis of GH deficiency, which was established by failure to respond to at least three stimulation tests. The first 6 days of hospitalization constituted a control period, during which a liquid diet that provided 9% of energy as high biologic-value protein was given. On day 6, tracer infusion studies were performed following an overnight fast. hGH (NPA) was then administered (0.1 U/kg/day, intramuscularly) between 10:00 P.M. and 11:00 P.M. and the studies were repeated on day 12.

The patients' weight and energy intake did not vary during the protocol. However, plasma urea nitrogen decreased significantly by the second day of hGH therapy. Urea synthesis also decreased significantly after 6 days of hGH therapy. Nitrogen excretion, determined by total stool and urinary nitrogen, was decreased, and this was accounted for by decreased urea excretion. The decrease in urea excretion was the result of decreased urea synthesis. Plasma glucose increased in eight of the 10 patients during hGH therapy, but there was no significant change in the rate of glucose turnover. There was no correlation between subsequent growth velocity while the patients were on hGH and the quantitative decrease of urea nitrogen during the acute administration of hGH.

Dahms WT, Owens RP, Kalhan SC, et al. *Metabolism* 1989; 38(3):197-203.

Editor's comment—*The authors state that previous studies have looked at the effect of GH on nitrogen balance using classic nitrogen balance studies. The present studies, however, demonstrate that the mechanism of the decrease in nitrogen secretion induced by GH is a decrease in urea synthesis. The authors further suggest that the most likely explanation for the decreased urea synthesis is the decreased production of ureagenic substrates by peripheral tissue, and state that the observed decreases in the plasma concentrations of the amino acids after hGH administration support this hypothesis. These carefully performed studies help to explain the changes that occur during GH administration. Unfortunately there was no correlation between the 6-month growth rate and the change in urea synthesis or blood urea nitrogen during the 7-day treatment.*

William L. Clarke, M.D.

Address for Correspondence

Please send all correspondence to
Robert M. Blizzard, M.D.
Department of Pediatrics
University of Virginia
School of Medicine
Charlottesville, VA 22908.

January 24, 1990 Endocrinology in Pediatric Practice, a one-day symposium. Garden City Hotel, Garden City, Long Island, New York. Contact: Denise DiSisto, Division of Continuing Education, Long Island Jewish Medical Center, New Hyde Park, NY 11042 (718-470-8650)

February 6-9, 1990 Joint Meeting of the Western Section of the American Federation of Research and the Western Society for Pediatric Research. Various locations in Carmel, California. Contact: David K. Stevenson, M.D., Department of Pediatrics, Room S222, Stanford University School of Medicine, Stanford, CA 94305 (415-723-5711)

May 7-11, 1990 Annual Meeting of the American Pediatric Society/Society for Pediatric Research/Ambulatory Pediatric Association. Hilton Hotel, Anaheim, California. Contact: Debbie Anagnospelis, Society for Pediatric Research, 2650 Yale Boulevard S.E., Suite 104, Albuquerque, NM 87106 (505-764-9099)

May 9, 1990 Diabetes Symposium, Lawson Wilkins Pediatric Endocrine Society. Hilton Hotel, Anaheim, California. Contact: Dr. Gilbert August, Children's Hospital, 111 Michigan Avenue N.W., Washington, DC 20010 (202-745-2121)

May 11, 1990 Annual Scientific Session Lawson Wilkins Pediatric Endocrine Society. Hilton Hotel, Anaheim, California. Contact: Dr. Gilbert August, Department of Endocrinology and Metabolism, Children's Hospital, 111 Michigan Avenue N.W., Washington, DC 20010 (202-745-2121)

June 8-11, 1990 30th Meeting of the Teratology Society. Empress Hotel and Convention Center, Vancouver, British Columbia. Contact: Ms. Alexandria Ventura, Teratology Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1841)

June 16-19, 1990 50th Annual Meeting and Scientific Sessions, American Diabetes Association. Georgia World Congress Center, Atlanta, Georgia. Contact: American Diabetes Association, 1660 Duke Street, Alexandria, VA 22314 (800-232-3472)

June 20-23, 1990 72nd Annual Meeting of The Endocrine Society. Convention Center, Atlanta, Georgia. Contact: Ann Singer, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

July 9-11, 1990 Annual March of Dimes Clinical Genetics Conference: Gastrointestinal Disorders. Westin Hotel, Detroit, Michigan. Contact: Orlando J. Miller, MD, Wayne State University, 2316 Scott Hall, 540 East Canfield Avenue, Detroit, MI 48201 (313-577-5323)

July 18-21, 1990 59th Annual Meeting of the Genetics Society of America (cohosted with the Genetics Society of Canada). San Francisco Hilton, San Francisco, California. Contact: Jean Francese, The Genetics Society of America, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1825).

October 12-14, 1990 31st Annual Meeting of the American College of Nutrition. Ramada Classic, Albuquerque, New Mexico. Contact: Kay Balun, American College of Nutrition, 345 Central Avenue, Suite 207, Scarsdale, NY 10543 (914-723-4247)

October 16-20, 1990 Annual Meeting of The American Society for Human Genetics. Convention Center, Cincinnati, Ohio. Contact: Notten Boom, Federation of American Societies for Experimental Biology, 9650 Rockville Pike, Bethesda, MD 20814 (301-530-7010)

October 28-November 1, 1990 42nd Annual Postgraduate Assembly of The Endocrine Society. Sheraton Waikiki, Honolulu, Hawaii. Contact: Ann Singer, The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814 (301-571-1802)

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Robert M. Blizzard, M.D.
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800 Second Avenue
New York, NY 10164-0569

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